S. HRG. 109–148

CROSSING THE VALLEY OF DEATH: BRINGING PROMISING MEDICAL COUNTERMEASURES TO BIOSHIELD

HEARING

BEFORE THE

SUBCOMMITTEE ON BIOTERRORISM AND PUBLIC HEALTH PREPAREDNESS

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS
UNITED STATES SENATE

ONE HUNDRED NINTH CONGRESS

FIRST SESSION

ON

EXAMINING PROMISING MEDICAL COUNTERMEASURES TO BIOSHIELD, FOCUSING ON THE PROJECT BIOSHIELD ACT OF 2004, AND THE ADMINISTRATION'S PRIORITY TO HAVE AN APPROPRIATE ARMAMENTARIUM OF MEDICAL COUNTERMEASURES AS A CRITICAL ASPECT OF THE RESPONSE AND RECOVERY COMPONENT OF THE PRESIDENT'S STRATEGY BIODEFENSE FOR THE 21ST CENTURY

JUNE 9, 2005

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C O N T E N T S

STATEMENTS

THURSDAY, JUNE 9, 2005

CROSSING THE VALLEY OF DEATH: BRINGING PROMISING MEDICAL COUNTERMEASURES TO BIOSHIELD

THURSDAY, JUNE 9, 2005

U.S. SENATE,
SUBCOMMITTEE ON BIOTERRORISM AND PUBLIC HEALTH PREPAREDNESS, COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:02 p.m., in room 430, Dirksen Senate Office Building, Senator Burr [chairman of the subcommittee] presiding.

Present: Senators Burr and Hatch.

OPENING STATEMENT OF SENATOR BURR

Senator BURR. The hearing will come to order. We will be joined periodically by other members of the subcommittee. It is indeed a good afternoon. I thank you for coming to our third hearing of the Health, Education, Labor, and Pensions Subcommittee on Bioterrorism and Public Health Preparedness.

I would like to call this hearing to order and welcome my colleagues, witnesses, and the interested parties to today's hearing, where we will examine the challenges our Nation faces in developing medical countermeasures for biodefense.

A little less than a month ago, I chaired a hearing of this subcommittee and during that, we examined the nature of the deliberate, accidental, and natural threat of biological agents. Since that time, we have had a very informative classified briefing by Porter Goss, Director of the CIA. His briefing served as an important reminder of al Qaeda's intent to use chemical and biologic weapons and the urgency of our efforts here today.

The insights gained from these sessions help give all of us a sense of what kinds of countermeasures we need to address the complex and diverse threat that we are faced with. It is apparent that in the future, we will need more broad spectrum countermeasures, like antivirals, and we need to create a capability to develop vaccines and other therapeutics faster.

The BioShield Act of 2004 has already done much to address our Nation's needs. For example, it has provided a guaranteed market for countermeasures and expedited NIH peer review practices to grant contracts and cooperative agreements. Both of these provisions have been used to purchase needed anthrax and smallpox

vaccines and treatments, as well as funded additional research into priority pathogens.

It is my assessment that so far, BioShield is meeting the needs of the near term threats from anthrax, smallpox, and botulism. What is not clear is how BioShield is positioned to address future threats and how we ensure that we can develop more and better medical countermeasures to address the contingencies of the future where surprise is likely to be the norm.

It is also not clear if the implementation of the BioShield Act has resulted in a predictable procurement process that ensures that companies and others know what kind of countermeasures the government and Nation needs and how much.

The subject of today's hearing is looking at the impediments to bring new countermeasures to the stockpile, or as a CEO of a biotech firm in Senator Kennedy's home State of Massachusetts called it potholes in the road to BioShield.

In Congress, we all take great satisfaction in the fact that we have ensured adequate funds are authorized and appropriated for basic research and development and that we have appropriated $5.6 billion for purchasing medical countermeasures for the Strategic National Stockpile. But I think there are potential gaps in our current approach that may need additional legislation, incentives, and possible resources.

What demands further examination is whether small and medium biotech companies are securing the resources to conduct the later stages of development and meet the necessary studies for safety and animal efficacy to be considered for BioShield.

I know in my home State of North Carolina, there are several companies like HemoCellular, EMD, and AlphaVax, and academic institutions like Duke University with promising approaches in technologies for biologic, chemical, and radiological countermeasures who have received NIH grants and/or DOD moneys who are now confronted by the valley of death of investment. I have heard informally from companies that their investors perceive biodefense research and development neutral or negative from an investment. It is my intent and that of the subcommittee to understand why that perspective exists and what we can do to change it.

I want to thank Senator Warner and his staff for facilitating the appearance of the Department of Defense today. It is not usual to have a DOD official come to the HELP Committee hearing, but for those who know DOD's history and current role in medical countermeasures research and development fully understand why there is a DOD witness. DOD's appearance today also highlights the important contribution that they have made and continue to make to homeland security. It is not always obvious, but DOD is always there.

Finally, I am also appreciative of the contributions made by my fellow committee members and their staff and Senator Enzi for his support and confidence.

I would like at this time to introduce both panels, if I may, and then we will proceed.

Dr. John Vitko is currently the director of Biological and Chemical Countermeasures for the Science and Technology Directorate

at the Department of Homeland Security. He is responsible for all DHS S&T activities to deter, detect, or mitigate a biological and chemical attack on people, infrastructure, or agriculture of this Nation.

Following Dr. Vitko, Dr. William Raub, who is the principal Deputy Assistant Secretary in the Office of Public Health Emergency Preparedness, Office of the Secretary of Health and Human Services. He will be presenting testimony representative of both HHS and NIH.

Dr. Raub is accompanied today by Dr. Carole Heilman, who is the current Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases at the National Institutes of Health. Both of you have extremely long titles. [Laughter.]

Finally, Dr. Joseph Palma is currently Medical Director, Office of the Deputy Assistant to the Secretary of Defense, Chemical/Biological Defense Programs, Office of the Secretary of Defense at the Pentagon—also a long title—responsible for research and development of medical countermeasures for the chemical/biological defense.

The second panel is composed of company, academic, and private experts who will provide their experience with medical countermeasure research and development and the challenges of getting products considered for BioShield procurement. From the company AVI BioPharma, we have the president and chief operating officer, Dr. Alan Timmins.

Dr. Richard Frothingham, who is an associate professor of medicine at Duke University with a dual appointment in the Department of Molecular Genetics and Microbiology.

Mr. David Wright is the president and chief executive officer of PharmAthene.

Major General Dr. Phillip Russell, Retired, U.S. Army, former senior advisor on BioShield issues in the Office of the Assistant Secretary for Public Health Emergency Preparedness at HHS.

And last but not least, Mr. Scott Magids, director of technology advancement programs from the University of Maryland.

Ladies and gentlemen, I want to thank you for your participation today. Without objection, all of my colleagues' opening statements will be a part of the record, so we won't have to stop and listen to any more of us talk up here.

It is indeed my honor to welcome all of you here, and with our first panel, I would recognize Dr. Vitko for his opening statement.

STATEMENTS OF JOHN VITKO, JR., DIRECTOR, BIOLOGICAL COUNTERMEASURES PORTFOLIO, SCIENCE AND TECHNOLOGY DIRECTORATE, U.S. DEPARTMENT OF HOMELAND SECURITY; WILLIAM F. RAUB, DEPUTY ASSISTANT SECRETARY, OFFICE OF PUBLIC HEALTH EMERGENCY PREPAREDNESS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY CAROLE HEILMAN, M.D., DIRECTOR, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH; AND COLONEL JOSEPH M. PALMA, M.D., MEDICAL DIRECTOR, OFFICE OF THE DEPUTY ASSISTANT TO THE SECRETARY OF DEFENSE FOR CHEMICAL AND BIOLOGICAL DEFENSE, U.S. DEPARTMENT OF DEFENSE

Mr. VITKO. Thank you, Chairman Burr. I am, in fact, very pleased to appear before you today to discuss the role the Department of Homeland Security's threat and risk assessments play in informing and prioritizing research and development of new medical countermeasures.

My oral comments will briefly discuss four key activities: Threat assessments and determinations conducted specifically to guide Project BioShield; a broader set of risk assessments to inform prioritization of all national biodefense activities; a strategy for addressing engineered threats, in partnership with and led by the Department of Health and Human Services; and scientific studies to better inform these assessments.

As you know, the Project BioShield Act of 2004 charges the Secretary of Homeland Security with the responsibility to determine which biological, chemical, radiological, or nuclear threats constitute a material threat to the security of our Nation. To fulfill this responsibility, DHS Science and Technology, in partnership with our Information Analysis and Infrastructure Protection Directorate, has been conducting formal threat assessments of the agents of greatest concern to establish plausible high-consequence scenarios. These assessments are then used by the Secretary of DHS in determining whether to issue a material threat determination or not, and by HHS and the Interagency Weapons of Mass Destruction Medical Countermeasures Subcommittee in determining the need for and requirements of any new medical countermeasures.

To date, the Secretary of DHS has issued material threat determinations for four agents, for anthrax, smallpox, botulinum toxin, and radiological nuclear devices. Additional assessments are currently underway for plague, tularemia, biohemorrhagic fevers, and chemical nerve agents. These will be completed later this fiscal year.

DHS has an even broader responsibility in the President's strategy for biodefense for the 21st century. In this strategy, we are charged with conducting formal periodic risk assessments in coordination with other departments and agencies to guide the prioritization of the Nation's ongoing biodefense activities, not just medical, but also including such areas as surveillance and detection, decontamination and restoration, and forensics. These risk assessments factor in technical feasibility of producing a broad range

of biological threats, the vulnerability of different portions of our society to those threats, and the resulting consequences of any attacks.

The first such formal risk assessment is due in the winter of 2006 and will address all Category A and B agents from the Centers for Disease Control and Prevention threat list, some Category C agents, and a number of potential engineered threats.

Recognizing that rapid advances in biotechnology demand that we also consider the possibility of engineered threats, we have partnered with HHS and others in formulating and implementing a strategy for anticipating and responding to such threats. Together, we have developed an informed estimate of the types of emerging threats that might be within the ability of a terrorist organization to develop over the near-, mid-, and longer-terms, and have laid out a strategy for addressing them. This strategy emphasizes ongoing technology watch and risk assessments, rapid surveillance and detection capabilities for engineered threats, an expanded range of medical countermeasures and the infrastructure to support them, and an integrated concept of operations for identifying and responding to emerging or engineered threats.

The threat and risk assessments that I have just described are performed with the best available information. However, I must tell you there are large uncertainties, sometimes factors of ten to 100, in some of the key parameters and, hence, in the associated risks. In one case, it can be the minimum amount of agent needed to affect a person. In another case, it can be the time that such an agent remains viable, that it is capable of causing an infection in the air, food, or water. And in a third, it can be the effect of food processing or water treatment on the agent's viability.

DHS has established a National Biodefense Analysis and Countermeasures Center, NBACC, to conduct the laboratory experiments needed to close these knowledge gaps. To support this, a new facility is being designed and constructed on a national interagency biodefense campus at Fort Detrick, Maryland. Pending the completion of this facility in fiscal year 2008, we have established an interim capability with other government and private laboratories to begin this line of work.

In summary, the Department of Homeland Security's Science and Technology Directorate, in coordination with its Federal partners, is conducting the threat and risk assessments that are critical to prioritizing the Nation's biodefense activities, including both near and longer-term medical countermeasures, research, and development.

This concludes my prepared statement. With the committee's permission, I request my formal statement be submitted for the record.

Mr. Chairman, I thank you for the opportunity to appear before you and I will be happy to answer any questions that you have.

Senator BURR. Thank you, Dr. Vitko, and without objection, everybody's entire statements will be part of the record.

Mr. VITKO. Thank you.

[The prepared statement of Mr. Vitko follows:]

PREPARED STATEMENT OF JOHN VITKO, JR.

Introduction

Good afternoon, Chairman Burr, Senator Kennedy and distinguished members of the subcommittee. I am pleased to appear before you today to discuss the role that the Department of Homeland Security's (DHS) threat and risk assessments play in informing and prioritizing research and development of new medical countermeasures.

Before focusing on the Department's specific activities in the area of threat and risk assessments, I would like to put these activities in the broader context of the overall responsibilities and activities of the DHS Biological Countermeasures Portfolio (Bio Portfolio). The mission of this Portfolio is to provide the understanding, technologies, and systems needed to anticipate, deter, protect against, detect, mitigate, and recover from possible biological attacks on this Nation's population, agriculture or infrastructure.

In addressing this mission, DHS has a leadership role in several key areas and partners with lead agencies in others. Those areas in which the Science and Technology (S&T) Directorate provides significant leadership are:

- Providing an overall end-to-end understanding of an integrated biodefense strategy, so as to guide the Secretary and the rest of the Department in its responsibility to coordinate the Nation's efforts to deter, detect, and respond to acts of biological terrorism.
- Providing scientific support to better understand both current and future biological threats and their potential impacts so as to guide the research and development of biodefense countermeasures such as vaccines, drugs, detection systems, and decontamination technologies.
- Developing early warning, detection, and characterization systems to permit timely response to mitigate the consequence of a biological attack.
- Conducting technical forensics to analyze and interpret materials recovered from an attack to support attribution.
- Operation of the Plum Island Animal Disease Center to support both research and development (R&D) and operational response to foreign animal diseases such as foot and mouth disease.

DHS also supports our partnering departments and agencies with their leads in other key areas of an integrated biodefense: the Department of Health and Human Services (HHS) on medical countermeasures and mass casualty response; the Department of Defense (DOD) on broad range of homeland security/homeland defense issues; the U.S. Department of Agriculture (USDA) on agriculture biosecurity; USDA and HHS on food security; the Environmental Protection Agency (EPA) on decontamination and on water security; the Department of Justice on bio-terrorism investigations; and the Intelligence Community on threat warnings.

Threat and Risk Assessments

As noted above, providing threat and risk assessments of both current and future threats and the scientific understanding to improve and refine these assessments is a major responsibility for DHS. These responsibilities are further defined in the BioShield Act of 2004, which charges the Secretary of DHS with the responsibility for determining which threats constitute a Material Threat to the national security or public health of the Nation and in the President's *Biodefense for the 21st Century* strategy, which charges DHS with the lead in "conducting routine capabilities assessments to guide prioritization of our ongoing investments in biodefense-related research, development, planning and preparedness".

Today, I would like to focus on four major activities that we have undertaken to fulfill these responsibilities:

1. Material Threat Assessments and Determinations in support of Project BioShield;
2. Risk Assessments to guide prioritization of the Nation's ongoing biodefense-related activities;
3. A Strategy for Addressing Emerging Threats (in partnership with the Department of Health and Human Services (DHHS) and others);
4. Scientific research to better inform these threat and risk assessments.

Material Threat Assessments and Determinations for Project BioShield

Working with the DHS Directorate for Information Analysis and Infrastructure Protection (IAIP), DHS S&T has been conducting assessments and determinations of biological, chemical, radiological and nuclear agents of greatest concern so as to guide near-term BioShield requirements and acquisitions. In this process, IAIP, in concert with other members of the intelligence community, provides information on

the capabilities, plans and intentions of terrorists and other non-state actors. However, since lack of intelligence on a threat does not mean lack of a threat, S&T, in concert with appropriate members of the technical community, also assesses the technical feasibility of a terrorist being able to obtain, produce and disseminate the agent in question. This information is used to establish a plausible high consequence scenario that provides an indication of the number of exposed individuals, the geographical extent of the exposure, and other collateral effects. If these consequences are of such a magnitude to be of significant concern to our national security, the Secretary of DHS then issues a formal Material Threat Determination to the Secretary of HHS, which initiates the BioShield process.

To date, the Secretary of DHS has issued Material Threat Determinations for four "agents": anthrax, smallpox, botulinum toxin, and radiological/nuclear devices. Additional threat assessments are underway for the remainder of the biological agents (plague, tularemia, viral hemorrhagic fevers) identified by the Centers for Disease Control and Prevention as Category A agents and for chemical nerve agents. These assessments will be completed this fiscal year.

Once a Material Threat Determination (MTD) has been issued, the HHS then assesses the potential public health consequences of the identified agent and determines the need for countermeasures. After notifying Congress of its determination, HHS evaluates the availability and appropriateness of current countermeasures and the possibility of development of new countermeasures. They are assisted in this by the interagency Weapons of Mass Destruction Medical Countermeasures (WMD-MC) subcommittee of the Office of Science and Technology Policy's National Science and Technology Council (NSTC). The WMD-MC further explores the medical consequences associated with the particular threat and the availability of appropriate countermeasures so as to develop a recommendation for the acquisition of a specific countermeasure. These recommendations then form the basis of the U.S. Government requirements. After approval of these requirements by the Office of Management and Budget, the HHS issues a Request for Proposals and implements and manages the subsequent acquisition process through delivery of the countermeasures to the Strategic National Stockpile.

Risk Assessments to Guide Prioritization of the Nation's Biodefense Activities

The preceding discussion dealt with threat assessments to guide BioShield acquisition processes. DHS has an even broader responsibility in the President's National Biodefense Strategy and that is to conduct formal, periodic risk assessments, in coordination with other Departments and agencies, to guide the prioritization of the Nation's ongoing biodefense activities—not just medical, but also including such areas as surveillance and detection, decontamination, and restoration, and forensics. These risk assessments provide a systematic look at the technical feasibility of a broad range of biological threats, the vulnerability of different portions of our society to those threats, and the resulting consequences of any such attacks.

The first such formal risk assessment is due in the winter of 2006, with subsequent assessments due every 2 years. The scope, process and timescale for this first assessment have been presented to and agreed to by the interagency Biodefense Policy Coordinating Committee co-chaired by the Homeland Security Council and the National Security Council. This assessment is addressing:

- All six category A agents from the Centers for Disease Control and Prevention (CDC) threat list;
- All 12 category B agents;
- Five representative category C agents; and
- A number of candidate drug-resistant and emerging agents.

Key outputs will include:

- A list of bio-threats prioritized by risk;
- A prioritized list of critical knowledge gaps that if closed should reduce risk assessment uncertainty and guide bio-defense research and development; and
- A list of biodefense vulnerabilities that could be reduced by countermeasure development and acquisition.

This risk assessment is being conducted in partnership with the Intelligence Community, the HHS, the Department of Defense, the U.S. Department of Agriculture, the Environmental Protection Agency, and others. Two advisory boards, one a Government Stakeholders Advisory Board and the other an Independent Risk Assessment Expert Review Board (academia, industry and government) have been established to provide input and advice.

This and subsequent risk assessments will play a critical role in informing future biodefense programs across all agencies, including BioShield acquisitions and the longer-term medical R&D leading up to such acquisitions.

A Strategy for Addressing Emerging Threats

Much of the biodefense efforts to date have focused on protecting against attacks with bioterrorism agents that can be (or used to be) found in nature. However, rapid advances in biotechnology demand that we also consider the possibility and impact of emerging or engineered agents. e.g. modifications to organisms that increase their resistance to medical countermeasure or make them more difficult to detect. The President's *Biodefense for the 21st Century* strategy assigns the HHS the lead in anticipating such future threats. We, DHS S&T, are partnering with HHS and others in formulating and implementing a strategy for anticipating and responding to such threats.

Based on intelligence information, available literature and expert judgment, we have developed an informed estimate of the types of emerging threats that might be within the ability of a terrorist organization to develop over the near (1–3 years), mid (4–10 years), and longer-terms (10 years). We have also examined the impact of these threats on the four pillars of the National Biodefense Policy: Threat Awareness, Prevention and Protection, Surveillance and Detection, and Response and Recovery.

In this analysis, four elements stand out as essential to an effective defense against emerging threats:

- Threat, vulnerability and risk assessments to prioritize these threats in terms of the difficulty of their development and deployment, as well as their potential consequences;
- Surveillance and detection capabilities to rapidly detect and characterize engineered agents in environmental and clinical samples so as to provide timely guidance in the selection of the appropriate medical countermeasure;
- An expanded range of safe and effective medical countermeasures and an infrastructure to support rapid research, development, test and evaluation (RDT&E) of new medical countermeasures; and
- integrated concepts of operation (CONOPS) for the identification and response to emerging threats. In addition to conducting these assessments, DHS will continue to collaborate with HHS as it leads efforts to anticipate emerging agents and to facilitate the availability of medical countermeasures.

Scientific Research to Better Inform These Threat and Risk Assessments

The threat and risk assessments described above are performed with the best available information. However, there are large uncertainties, sometimes factors of ten to a hundred, in some of the key parameters and hence in the associated risks. One of the major functions of the threat and risk assessments is to identify these critical knowledge gaps, which can differ for different threat scenarios—in one case it can be the minimum amount of agent needed to infect a person; in another case it can be the time that such an agent remains viable (capable of causing an infection) in the air, food or water; and in a third it can be the effect of food processing or water treatment on the agent's viability. Conducting the laboratory experiments to close the critical knowledge gaps is a primary function of DHS's National Biodefense Analysis and Countermeasures Center (NBACC).

Congress has appropriated a total of $128M for design and construction of NBACC with the necessary biocontainment laboratory space and support infrastructure to conduct these and other experiments. NBACC will be built on the National Interagency Biodefense Campus (NIBC) at Ft. Detrick MD, where its close physical proximity to the DOD's U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID), the NIH's Integrated Research Facility and the USDA's Foreign Disease-Weed Science Research Unit. NBACC is also collaborating with the Centers for Disease Control and Prevention to further address the critical knowledge gaps. The Record of Decision for NBACC's Final Environmental Impact Statement was signed in January 2005. Design of the facility began in March 2005, with construction scheduled to begin in fiscal year 2006 and be complete by the fourth quarter of fiscal year 2008.

Currently, interim capabilities for both NBACC's biological threat awareness and bioforensic analysis functions have been established with other government and private laboratories to allow vital work in these areas to occur during the NBACC facility's construction.

Conclusion

The DHS Science and Technology Directorate's programs in threat and risk assessment, and in the supporting science, play a critical role in prioritizing the Nation's biodefense activities, including both near and long-term medical countermeasures research and development. These threat and risk assessments are conducted in active collaboration with other Federal departments and agencies and

with the appropriate technical experts in the government, academia, and the private sector as we collectively seek to reduce the threat of a biological attack against this Nation's population, its agriculture and its food supply.

This concludes my prepared statement. With the committee's permission, I request my formal statement be submitted for the record. Mr. Chairman, Senator Kennedy, and members of the subcommittee, I thank you for the opportunity to appear before you and I will be happy to answer any questions that you may have.

Senator BURR. Dr. Raub.

Mr. RAUB. Thank you, Mr. Chairman. Dr. Heilman and I appreciate the opportunity to share with you information on our progress in implementing the Project BioShield Act of 2004 as we approach the first anniversary of its enactment. With your permission, I will submit my full statement for the record.

HHS shares the subcommittee's desire to foster the emergence of new or improved medical countermeasures against terrorism, and we share the subcommittee's concern about the obstacles that can retard the maturation of promising concepts into licensed or approved products. In particular, we are eager to ensure that funding is available for meritorious, high-priority countermeasure candidates at every stage of the research, development, acquisition spectrum.

HHS has two funding mechanisms with which to pursue this objective. The National Institute of Allergy and Infectious Diseases of the NIH funds countermeasure-related activities as needs and opportunities dictate, from basic research to advanced development, including scale-up from benchtop to commercial production methods and clinical trials of investigational products for safety and efficacy. The HHS Office of the Assistant Secretary for Public Health Emergency Preparedness, using the BioShield Special Reserve Fund, sponsors, as appropriate, the final stages of advanced development, attainment of licensure or approval, and acquisition of completed product for addition to the Strategic National Stockpile.

Used together in a carefully coordinated way, these two mechanisms can do much to ensure that meritorious candidate products, whether still at the laboratory stage or already into clinical trials, can find the support necessary to reveal and assess their full potential.

The quest for a second generation anthrax vaccine based on a recombinant version of the protective antigen of the anthrax organism, Bacillus anthraces, illustrates the utility of this concept. Building upon the pioneering work of the United States Army Medical Research Institute of Infectious Diseases, the NIH contracted for the early and advanced development of a recombinant protective antigen, or RPA, vaccine in September 2002 and 2003, respectively. These milestone-driven contracts contained well-defined deliverables, including the manufacture of clinical-grade vaccine, the conduct of Phase I and Phase II clinical trials, and consistency lot manufacturing of vaccine.

In March 2004, the HHS Office of Public Health Emergency Preparedness employed the BioShield Special Reserve Fund to launch a competitive acquisition of 75 million doses of the vaccine. This contract features a milestone and deliverables approach, which includes a requirement for the delivery of the first 25 million vaccine doses in single-dose, ready-to-use syringes to the Strategic National Stockpile within 2 years of contract awards. A noteworthy aspect

of this contract is the fact that no payment will be made until usable product is delivered to the stockpile.

A similar scenario is in mid-course with respect to development and acquisition of a second generation smallpox vaccine. Modified Vaccinia Ankara, or MVA, is based on a strain of the Vaccinia virus that, in contrast to the current smallpox vaccines, such as Dryvax, does not replicate effectively in human cells and, thus, may cause fewer side effects. The NIH supported the development of MVA vaccine with milestone-driven contract awards in 2003 and 2004. Early clinical trials have demonstrated that MVA vaccine is safe and immunogenic in human volunteers, and animal studies by the developers are confirming earlier studies by NIH and DOD scientists showing that MVA vaccine protects monkeys and mice from smallpox-like viruses.

Based on these results and the demonstration of the feasibility of large-scale manufacturing capability, the Office of Public Health Emergency Preparedness is moving forward with an MVA vaccine acquisition program using the Bioshield Special Reserve Fund. Last month, HHS released a draft request for proposals for industry comments. Formal solicitation of competitive contract proposals is slated for this summer.

Future countermeasure development efforts undoubtedly will present their own special challenges and may not follow the path being used for the RPA and RVA vaccine.

We remain committed to working closely with our colleagues within HHS, across the Federal Government, and within academia and industry toward acquiring needed countermeasures as rapidly as possible, and we remain committed to making the best use of the authorities and resources available to us and to refining our mechanisms based on lessons learned.

I will be pleased to respond to your questions as best I can.

Senator BURR. Dr. Raub, thank you so much.

[The prepared statement of Mr. Raub follows:]

PREPARED STATEMENT OF WILLIAM F. RAUB, PH.D.

Good afternoon, Mr. Chairman, Senator Kennedy and subcommittee members. I am William Raub, Deputy Assistant Secretary for Public Health Emergency Preparedness, Department of Health and Human Services (HHS). I am here with my colleague, Dr. Carole Heilman, Director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). We appreciate the opportunity to share with you information on our progress in implementing the Project BioShield Act of 2004, which was enacted in July 2004. Biodefense is a top priority for the Bush administration and having an appropriate armamentarium of medical countermeasures is a critical aspect of the response and recovery component of the President's strategy "Biodefense for the 21st Century." The acquisition and ready availability of medical countermeasures, such as antibiotics, antivirals, monoclonal and polyclonal antibodies against infectious threats; therapies for chemical and radiation-induced illnesses; and vaccines to protect against biological agents and toxins will have a substantial impact on our preparedness and response capabilities.

Protecting Americans

The events of September and October 2001, made it very clear that terrorism—indeed bioterrorism—is a serious threat to our Nation and the world. The Bush administration and Congress responded forcefully to this threat by seeking to strengthen our medical and public health capacities to protect our citizens from future attacks. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 substantially increased funding authorization for the Centers for Disease Control and Prevention's (CDC's) Strategic National Stockpile. To encourage

the development of new medical countermeasures against biological, chemical, radiological and nuclear agents and to speed their delivery and use in the time of an attack, President Bush, in his 2003 State of the Union address, proposed, and Congress subsequently enacted, the Project BioShield Act of 2004. Project BioShield authorized the use of the Special Reserve Fund created in the first Department of Homeland Security (DHS) appropriation bill (P.L. 108–90) in October 2003. This $5.6 billion appropriation is designed to assure developers that funds will be available to purchase critical medical countermeasures to protect our citizens. In addition, over $5 billion in biodefense funding was appropriated to NIH between fiscal year 2002 and fiscal year 2005. These funds have provided significant support of research and development of safe and effective medical countermeasures.

The Strategic National Stockpile Today

The wake-up call that we received in the fall of 2001 brought clarity to the gaps in our medical countermeasure armamentarium and we immediately sought to address these gaps. Although much remains to be done, we have made significant progress in building our Strategic National Stockpile (SNS). For example, our smallpox vaccine stockpile has grown from 90,000 ready-to-use doses in 2001 to enough vaccine to protect every man, woman, and child in America. Major strides have been made in building our medical countermeasure antibiotic reserve against anthrax, plague, and tularemia. The SNS now contains countermeasures to protect and treat millions of Americans in the event of an attack with one of these agents. We have also built our stockpile of countermeasures to address the effects of radiation exposure with products such as Prussian Blue and diethylenetriaminepentaacetate (DTPA). These countermeasures act to block uptake or remove radioactive elements such as cesium, thallium, or americium from the body. Potassium iodide, a drug that can protect the thyroid from the harmful effects of radioactive iodine, is also stockpiled in formulations that will protect both adults and children. Furthermore, under Project BioShield, HHS is acquiring licensed and next-generation anthrax vaccines as well as anthrax antitoxins to further enhance our capabilities to respond to that threat. We have taken the botulinum antitoxin research program started by the Department of Defense (DOD) in the early 1990s to completion and we are now in the process of adding to our stockpile of botulinum antitoxins.

Ongoing Project BioShield Activities at NIH and HHS

The Project BioShield Act of 2004 created several mechanisms to help the U.S. Government (USG) address gaps in the medical countermeasures development pipeline. These mechanisms include new authorities for the NIH to expedite the research and development of promising medical countermeasures in advance of the acquisition of these countermeasures through the Project BioShield.

Last month, the NIAID announced the first awards made using its new BioShield authorities. These awards included 10 grants and two contracts totaling approximately $27 million to support the development of new therapeutics and vaccines against some of the most deadly diseases that could be caused by bioterrorism, including anthrax, botulism, Ebola hemorrhagic fever, pneumonic plague, smallpox, and tularemia. These grants and contracts, which range in duration from 12 to 18 months, respond to a key objective of the NIAID biodefense research agenda that emphasizes the development of new and improved medical products against agents identified by the CDC as Category A agents, those deemed to pose the gravest threat.

In addition to these medical countermeasures development contracts, several BioShield procurement activities are underway at HHS. The Office of Public Health Emergency Preparedness (OPHEP) is reviewing the responses to Requests for Proposals (RFPs) for anthrax therapies, and is continuing to move forward on the acquisition of an antitoxin treatment for botulism. Furthermore, OPHEP has signaled its intent to acquire a next generation smallpox vaccine by releasing a draft RFP for industry comment. The smallpox vaccine development and acquisition program exemplifies the strong partnership between NIAID and OPHEP for this medical countermeasure. This development program has been closely monitored within HHS, and the requirements and options for acquisition were developed by the interagency Weapons of Mass Destruction (WMD) Medical Countermeasures subcommittee.

Finally, in anticipation of yet-to-be-determined requirements, OPHEP, in coordination with colleagues throughout the USG, actively monitors the state of the medical countermeasure pipeline—both within and outside the government—by evaluating USG research and development portfolios and engaging industry through the publication of Requests for Information (RFIs). For example, OPHEP has released three RFIs to assess the timeline to maturity of medical countermeasures to treat

nerve agent exposure, acute radiation syndrome, and additional products that might be available to treat anthrax. These RFIs are a key tool for HHS to dialogue with industry partners and to inform the development of sound USG acquisition strategies.

Development of Medical Countermeasures

These accomplishments in acquiring needed countermeasures for the Strategic National Stockpile were possible in large part because of substantial existing research and development of countermeasures in these key areas. The development of medical products—whether for cancer, influenza, or anthrax—is a complex, lengthy, and expensive process. An overview of the key features and challenges of the medical countermeasure pipeline from concept to regulatory approval may be helpful to understand the complexity of the process.

Steps in Medical Product Development

The initial stage in the medical countermeasure pipeline is a robust basic research program. The milestones at this stage include a fundamental understanding at the molecular level of host-pathogen interactions, the pathogenicity of the threat agent, identification of targets of opportunity for preventing or mitigating the consequences of the threat agent, and determining the mechanism of action of potential medical countermeasure candidates. The following stage is described as applied research; here, candidate products are identified and screened for activity against a threat agent, and animal models are developed. In the development stage, processes are established to manufacture the product using current Good Manufacturing Practices (cGMP) and human clinical Phase I and Phase II trials are conducted. These clinical trials and additional animal efficacy studies enable the determination of optimal formulation and dosage schedules. In addition, the stability profile is evaluated and a large-scale, validated manufacturing processes with requisite quality control/quality assurances is established. In the final development stage, production and licensure, Phase III trials and pivotal animal studies are completed. Ultimate licensure, approval or clearance from the U.S. Food and Drug Administration (FDA) requires the rigorous accumulation of sufficient data in humans and animals to establish the safety and efficacy of the product and the ability to consistently manufacture the product to meet the standards of cGMP. It is important to note that a unique aspect of the pathway for medical countermeasures is the need to establish efficacy either using surrogate markers (such as the human immune response) or, using appropriate animal models, under the "Animal Rule" because demonstration of efficacy against the actual diseases in humans is most often not feasible either because the disease does not occur naturally or for the obvious ethical reasons that prevent exposing humans to the threat agent.

Challenges to Product Development

The pathway from medical product concept to a safe, effective, and reliably manufactured product suitable for regulatory approval can be a long and expensive one. Studies indicate that each new product brought to market can take up to a decade of development and up to a billion dollars of investment; the overwhelming number of candidates will fail before one is found that demonstrates sufficient evidence of safety and efficacy to justify approval, licensure or clearance by the FDA. For example, a new drug compound entering Phase I testing, often representing the culmination of upwards of a decade of preclinical evaluation, is estimated to have only an eight percent chance of reaching the market.

The Strategic Approach to Addressing Medical Countermeasure Gaps

With the critical path for medical countermeasures in mind, the USG has taken a strategic approach to the development and acquisition of these countermeasures. The initial focus of our efforts to protect the Nation was aimed largely at those threats that could do the greatest harm to the greatest number of our citizens, namely, smallpox and anthrax. Our national security environment demands accelerated product development timelines and new paradigms of interactions between industry and government with increased risk-sharing and enhanced intra-governmental collaboration. Using a robust interagency process that mined intra- and extra-governmental expertise, requirements for medical countermeasures were identified, and options elaborated for addressing immediate and long-term needs. In addition, there have been substantial interagency efforts within HHS to examine and address gaps in the pipeline. Experts from throughout HHS and USG continue to define the most expeditious way to traverse the critical pathway to develop and acquire safe and effective medical countermeasures for the Strategic National Stockpile. This approach is focused on identifying and addressing gaps in this critical pathway.

Addressing Critical Countermeasure Gaps for Anthrax and Smallpox

The USG actions taken to fill gaps in our anthrax and smallpox armamentarium best illustrate the outcome of our strategic approach in the development medical countermeasures and the implementation of the Project BioShield Act of 2004.

Anthrax

Although anthrax is not transmissible from person-to-person, an attack involving the aerosol dissemination of anthrax spores, particularly in an urban setting, is considered by public health experts to have the potential for catastrophic effects. The potential for large-scale population exposure following aerosol release of anthrax spores, the reality of the threat demonstrated by the anthrax letters of October 2001, and our knowledge that anthrax has been weaponized by state-actors, highlight the nature of the threat. Following the process established by Project BioShield, the Secretary of the Department of Homeland Security (DHS) determined that anthrax posed a material threat to the Nation, and, because untreated inhalation anthrax is usually fatal, the Secretary of HHS identified anthrax as a significant threat to public health. It is for these reasons that three of the first six acquisition programs under Project BioShield have been targeted to address this pathogen.

The approach to protect citizens against this threat demanded immediate, intermediate and long-term strategies and requirements. The NIH and HHS are working aggressively to address the requirements, many of which are defined by the interagency WMD Medical Countermeasures Subcommittee. These requirements are informed by material threat assessments provided by the DHS. First, the existing stockpile of antibiotics against anthrax in the Strategic National Stockpile was increased. Second, there is a need for an anthrax vaccine to be used not only for preexposure protection for laboratory and other workers at known risk for anthrax, but also for use concurrently with antibiotics after an exposure. Anthrax spores are stable in the environment and would have a profound impact if released in an urban population. Availability of an anthrax vaccine is a critical requirement for restoring the functionality of any exposed area. Finally, an anthrax vaccine and anthrax therapeutics such as antitoxins would provide for protection and treatment of individuals exposed to an engineered strain of anthrax that may be resistant to antibiotics.

In a 2002 report, "Anthrax Vaccine: Is It Safe? Does it Work", the Institute of Medicine recommended that a new vaccine be developed according to more modern principles of vaccinology. To address this gap, NIH convened experts in the fall of 2001 to assess developing technologies. Based on their review, HHS decided that there was a sufficient scientific foundation to support the aggressive development of a next generation anthrax vaccine consisting of recombinant protective antigen (rPA). The research on rPA, spanning more than a decade, was conducted in large part by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, MD.

HHS defined a three-stage development and acquisition strategy to address the gaps in anthrax countermeasures through a public-private partnership model using open competition for awards at each stage. The early and advanced development programs for rPA were supported by the NIAID with contract awards in September 2002 and 2003, respectively. These were milestone-driven contracts with well-defined deliverables including the manufacture of clinical-grade vaccine, the conduct of Phase I and Phase II clinical trials, and consistency lot manufacturing of vaccine. Demonstrated large-scale manufacturing capability would be required to support the initial civilian acquisition target for rPA, which was defined through an interagency process to be the protection of 25 million persons. Senior officials from several Departments of the USG evaluated acquisition options to fulfill this target and, in the fall of 2003, agreed to pursue this acquisition of rPA anthrax vaccine.

An evaluation of the NIAID rPA anthrax vaccine development program indicated that it was robust enough to suggest that rPA vaccine could potentially become a licensed product within eight years. In March 2004, the acquisition program for this vaccine, under the direction of the OPHEP, was launched, relying on the Special Reserve Fund. Utilizing a robust technical and business evaluation process, OPHEP reviewed multiple proposals and negotiated a contract for 75 million doses of the vaccine. This contract uses a milestone and deliverables approach to lay out an ambitious program which includes the delivery of the first 25 million vaccine doses to the Strategic National Stockpile within 2 years of contract award. A unique and critical aspect of the rPA vaccine BioShield acquisition contract is the fact that no payment will be made until a usable product is delivered to the Stockpile. While awaiting delivery of this new vaccine to the Stockpile, OPHEP negotiated a contract for five million doses of the currently licensed anthrax vaccine to support immediate

requirements. Delivery of that product to the Stockpile has already begun. Over one million doses of the licensed anthrax vaccine are now in the Stockpile.

Smallpox

A similar three-stage development and acquisition strategy was utilized to address the gap regarding a next generation smallpox vaccine. The interagency WMD Medical Countermeasures Subcommittee defined a requirement for this product that addressed the millions of U.S. citizens who have contraindications for the existing smallpox vaccines in the absence of exposure to smallpox. One candidate next-generation smallpox vaccine, modified vaccinia Ankara (MVA), is based on a strain of the smallpox vaccine virus that, in contrast to current smallpox vaccines such as Dryvax, does not replicate effectively in human cells and may cause fewer side effects. The development programs for MVA were supported by the NIAID with milestone-driven contract awards in 2003 and 2004. Early clinical trials in limited numbers of human volunteers have demonstrated the MVA vaccine to be safe and immunogenic, and animal studies by the developers are confirming earlier studies by NIAID and DOD scientists showing that MVA protects monkeys and mice from smallpox-like viruses. Based on these results and the demonstration of the feasibility of large-scale manufacturing capacity, HHS has moved forward with the initial stages of an MVA acquisition program. A draft RFP was released last month; the final RFP will be released following review of industry comments.

Priority Setting Beyond Smallpox and Anthrax

The approach taken to rapidly expand our Nation's response capacity to meet the medical and public health impact of either a smallpox or anthrax attack demonstrate our national resolve to address these high priority threats. However, in many ways, anthrax and smallpox vaccines represent the "low hanging fruit" for medical countermeasure research; development and acquisition were enabled by a substantial research base developed by USAMRIID and NIH. There was consensus that these were our highest priorities and there were countermeasures available or relatively far along in the development pipeline to permit acquisition for the SNS. Given an almost endless list of potential threats and with finite resources to address them, prioritization of these threats and appropriate countermeasures is essential to focus our efforts. We rely heavily upon our interagency partner, the DHS, to provide us with a prioritized list of threats along with material threat assessments that will provide reasonable estimates of population exposure. This information is critical for future strategic decision making regarding how best to focus our National efforts in countermeasure development and acquisition, including whether in the short-term, the so-called "one-bug, one-drug" approach should continue while simultaneously investing in more broad-spectrum prevention and treatment approaches for the longer term. These issues are actively being addressed by the interagency WMD Medical Countermeasures Subcommittee.

Coordinating Efforts to Fill Gaps in the Critical Path to Needed Countermeasures

HHS is strengthening existing intra and interagency partnerships and creating new ones that are needed to address identified gaps in the Nation's medical countermeasure research, development, and acquisition pipeline. A key collaboration is between OPHEP and NIAID, with contributions from FDA in high priority areas. Senior scientific and policy staffs from these organizations meet regularly to discuss identified gaps and outline strategies to address these gaps using existing institutional structures and resources.

Addressing Medical Countermeasure Gaps for Chemical and Radiological/ Nuclear Threats

For the development of medical countermeasures to address chemical, radiological and nuclear threats, OPHEP, NIH and FDA have established a unique partnership in which experts from these organizations meet on a regular basis to identify appropriate targets and conduct joint planning that ensures the alignment of development and acquisition priorities.

In 2004, HHS tasked NIAID with developing a research program to accelerate the development and deployment of new medical countermeasures against ionizing radiation for the civilian population. NIAID worked to build upon prior experience and ongoing research efforts as it gathered input from across the USG as well as from experts in industry and academia to inform the development of a planning document, entitled *The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats.* This document is in the final stages of production and will be made available shortly.

This *Strategic Research Plan and Agenda* is organized into four sections: (1) basic and translational research on the mechanisms of radiation injury, repair, and res-

toration that can lead to the identification and characterization of new therapeutics; (2) bioassays and tools for biodosimetry, which will aid in diagnosis; (3) immediate product development of promising therapies; and (4) infrastructure to support the necessary research. The document is intended to unify and strengthen the research community focused on these areas, promote increased collaboration, and facilitate transition from research to product development. NIH will work closely with OPHEP to prioritize the research and development activities to align with the priorities for acquisition under Project BioShield.

The fiscal year 2005 funding for NIH radiation countermeasures research is $47 million; these funds are provided through an appropriation to OPHEP. A proposal for specific project commitments was submitted by NIH and reviewed and approved by OPHEP. Proposed projects include:

- a network of research facilities called the Centers for Medical Countermeasures for Radiation;
- contracts to support the development of orally-available forms of calcium and zinc DTPA, which enhance the excretion of certain radionuclides that would be released by a nuclear device or as a result of an attack on a nuclear reactor;
- a contract to support a broad range of product development activities;
- an interagency partnership with the Armed Forces Radiobiology Research Institute of the DOD; and
- an initiative to support projects that explore ways to protect the immune system from radiation damage.

This program will be guided by a Program Management Team comprised of representatives from NIH and OPHEP. The projects will be directed by staff in NIAID's Division of Allergy, Immunology, and Transplantation.

Similarly, NIH was tasked by HHS to draft a strategic plan and research agenda to guide the development of medical countermeasures against chemical threats. In fiscal year 2006, $50M from the Public Health Social Services Emergency Fund is requested for this purpose. Following the oversight and planning model established for radiological and nuclear medical countermeasures, a Program Management Team with representatives from NIH and OPHEP will be established and a spending plan will be developed prior to the allocation of funds. Some of the objectives targeted for development will include anti-seizure medications, rapid diagnostics, animal models and decontaminants. A Strategic Plan and Research Agenda from NIH is expected to be completed by the end of this calendar year.

Novel and Emerging Threats

The initial efforts for medical countermeasure development and acquisition have been rightfully focused on those threat agents known to have the potential to cause catastrophic effects on our Nation and its citizens. In addition, HHS and NIH are keenly aware of, and invest efforts to address threat agents that we might face in the future, including engineered threats.

As is also the case for the known threat agents, we are dependent upon our colleagues at DHS to identify and prioritize these threats. One of the most recognized potential engineered threats is antibiotic-resistant anthrax, and the HHS, NIH and FDA accomplishments to date in facilitating the development and acquisition of anthrax vaccines and therapeutic antitoxins have an important beneficial impact on reducing our vulnerabilities. In addition, NIH has a robust investment in the development of novel antimicrobial agents and in addressing all aspects of antibiotic resistance, including the development of antibacterial agents that could potentially be useful against a broad spectrum of species and a wide range of drug resistance mechanisms and is working with the DOD, to leverage medical countermeasure programs and resources of mutual interest. Several medical countermeasures now being developed through NIAID for civilians have their technology basis in programs which originated in DOD.

One major NIAID basic biodefense research initiative is focused on the human innate immune system, which is comprised of broadly active "first responder" cells and other non-specific mechanisms that are the first line of defense against infection. The development of methods to boost innate immune responses could lead to the development of a relatively small set of fast-acting countermeasures that would be effective against a wide variety of pathogens, including engineered threat agents.

Conclusion

In closing, I must emphasize that the number of threat agents against which we could guard ourselves is endless. New and emerging threats introduced by nature or by design will present continuing challenges. Although we cannot be prepared for every threat, we have the ability to create a strategic approach to identifying and combating the greatest threats through the development and availability of safe and

effective medical countermeasures. HHS and its agencies, including NIH, CDC, and FDA, have a clear mandate from President Bush and Congress to lead the charge in this arena and in the implementation of Project BioShield. The tightly orchestrated development, acquisition, and review programs for next generation anthrax and smallpox vaccines outlined here are outstanding demonstrations of the USG support and management of a medical countermeasure program throughout the development pipeline.

We have already made important strides and will continue to work to address the obstacles identified. Mr. Chairman, I look forward to working with you and members of the subcommittee to address the challenges of bioterrorism preparedness and its impact on public health.

We will be happy to answer any questions you may have.

Senator BURR. Dr. Heilman, do you have any opening statements to make?

Dr. HEILMAN. No, I don't.

Senator BURR. Great. Dr. Palma.

Dr. PALMA. Chairman Burr, members of the subcommittee, and fellow colleagues, I am honored to appear before your subcommittee. I am Colonel Joseph Palma. I am Medical Director within the Office of the Assistant Secretary of Defense for Chemical and Biological Defense and I would like to provide information on three particular issues.

The Department of Defense is involved in biodefense, and those are the efforts to develop promising new medical countermeasures to biological threats, concerns related to the transition of candidate technologies to the point where BioShield authorities can be used to fund procurement, and I would like to share some thoughts on the perceived "Valley of Death" issues that we have been grappling with for some time.

The role of our program is to oversee all of the Department of Defense's chemical and biological defense programs, not just the medical ones, but I recognize that today's hearing is only about the medical countermeasure for biodefense. In accordance with Congressional authority, Dr. Kline, the Assistant to the Secretary, is the single point of contact for the Department to which we report on these efforts.

To support biodefense and WMD defense against weapons of mass destruction, the Secretary provided direction to us earlier this year to do an analysis of the requirements that were needed for the Department of Defense to have novel medical countermeasures, and novel countermeasures, in general. Senior leaders agreed after that to plus-up our program by $2.1 billion additional for the fiscal years 2006–2011, bringing the budget up to about $10 billion.

In addition to the study, the Director of Program Analysis and Evaluation identified an additional $100 million in fiscal year 2006 uniquely to start addressing as a downpayment biological warfare medical countermeasures that address bioengineered threats. These medical countermeasures initiatives will apply transformational approaches leveraging genomics, proteonomics, systems biology, immunology, and bioinformatics for the purpose of creating a more responsive and agile set of countermeasures that leverage these maturing technologies.

The chemical biodefense program has made progress in the last several years in biodefense, and I will just mention a few of the more recent examples. In February of this year, the FDA approved the DOD vaccine immunoglobulin to treat adverse effects of small-

pox immunization. In early 2005, clinical trials began for both multivalent Botulinum vaccine for serotypes A and B and a plague vaccine. In July, clinical trials will begin for Venezuelan equine encephalitis vaccine. We have been working diligently to create a multiagent vaccine where we are leveraging some of the industry and biotechnology companies, AlphaVax being one of them.

On top of this long history of biodefense, we have a very long history of successes that do stop at the Valley of Death because of the funding constraints and the capitalization shortfalls.

The DOD Chemical and Biological Defense Program activities are coordinated, however, with the Department of Health and Human Services and the National Institutes of Health as well as the Centers for Disease Control and Prevention. We are on the verge of actually finalizing formal interagency agreements regarding cooperation in medical countermeasure development.

It is important to note that some of those medical countermeasures currently being developed through the National Stockpile have their technology bases on programs originated in DOD, such as the next-generation anthrax vaccine and the smallpox vaccine currently being developed, as well as the science that currently informs Botulinum antitoxin development.

A critical aspect of interagency coordination is support of BioShield. Dr. Kline testified in April of 2003 that the Department supported BioShield. It is important that military and civilian capabilities and concept of use and medical countermeasures, it is important to understand these requirements don't always coincide. The medical capability requirements generally focus on pre-exposure, prophylaxis for a smaller and more defined population. Civilian requirements tend to focus on postexposure prophylaxis and treatment for a larger and more diverse population, such as geriatrics and pediatrics. The route of administration sometimes also differs.

Since this is a hearing on the Valley of Death, I would like to give you a little bit of our perspective in this area. As a preamble, we would like to define the Valley of Death as a step between R&D and commercialization. It applies to all products, of which biologics is only one, and has some unique challenges. Fewer than one in 100 candidates will receive approval by the FDA, and once a product receives FDA approval, it can take, in our estimation, between eight and 10 years and $500 to $800 million to bring it to market.

We are looking—and the issues there, the challenges are candidate exploration, which is the discovery phase, efficacy and toxicity studies, whether they work out or not, scale-up production sorts of issues, lack of infrastructure, process development and definitization so that it works.

We are looking at ways to speed up overall development process for licensure of potential medical countermeasures, which can take quite a long time. We believe the most promising savings will probably occur in the initial phases, the 2- to 5-year period of candidate discovery, because the more candidates you have, the more likely you are to find the successful ones. With adequate funding, manufacturing capabilities, and required biocontainment facilities, especially for the animals tested that needs to be done, the safety and toxicology testing may also be accelerated.

Within DOD, our medical countermeasure development process is requirement driven, so we tend to fund those issues that are successful for us and we try and put all the efforts against it, but we do have to prioritize. We don't believe, however, fast-track authority at the FDA will necessarily shorten our ability to do that.

Thank you for the opportunity to address these issues, sir. I will try to address any additional concerns or questions the subcommittee may have.

Senator BURR. Dr. Palma, thank you very much.

[The prepared statement of Dr. Palma follows:]

PREPARED STATEMENT OF COLONEL JOSEPH PALMA, M.D., USAF

Chairman Burr, Senator Kennedy and members of the subcommittee: I am honored to appear before your subcommittee. I am Colonel Joseph Palma, the Medical Director within the Office of the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense. I will provide information on Department of Defense efforts to develop promising new medical countermeasures to chemical, biological, radiological, and nuclear (CBRN) threats. I will also address concerns related to the transition of candidate technologies to the point where BioShield Act authorities can be used to fund the procurement. I will also share my thoughts on the perceived "Valley of Death" related to drug development. Following my comments, I welcome any questions the subcommittee may have and I will do my best to answer them.

DOD Chemical and Biological Defense Program—From Strategy to Programs

In accordance with congressional authority, the Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs serves as focal point overseeing the Department's chemical and biological defense research, development, and acquisition. In preparation of the Fiscal Year 2006 President's Budget Submission for the Department's Chemical and Biological Defense Program, we used a new process based on the program reorganization that occurred in 2003. This improved process ensures that the Department's efforts in CBRN defense are closely aligned with strategic guidance and are driven by operational requirements, rather than being driven by technological approaches.

The planning process for the budget begins with the *National Security Strategy,* which establishes the position of the United States and outlines the defense strategy. Drawing from the direction and goals in NSS, the Joint Chiefs of Staff prepare and present the *National Military Strategy.* The *National Military Strategy* recommends military objectives and strategy, fiscally constrained force levels, and force options; and provides a risk assessment for programs.

A major aspect of the planning phase is the Joint Capabilities Development process. The Joint Capabilities Development approach to defense planning serves to focus attention on required capabilities while providing guidance to fit programs within the resources available and meet the defense goals. As stated in the guidance, a key Strategic Objective for the Department is to *Secure the United States from Direct Attack*—We will give top priority to dissuading, deterring, and defeating those who seek to harm the United States directly, including those extremist individuals or organizations that may possess and employ weapons of mass destruction.

The current CBRN Defense strategy emphasizes a capabilities-based approach rather than the previous approach, which provided greater emphasis on prioritizing threat agents and targeting budgetary resources based on validated intelligence. Capabilities-based planning focuses more on how adversaries may challenge us than on whom those adversaries might be or where we might face them. It reduces the dependence on intelligence data and recognizes the impossibility of predicting complex events with precision. This strategy drives a top-down, competitive process that enables the Secretary to balance risk across the range of complex threats facing military personnel, to balance risk between current and future challenges, and to balance risk within fiscal constraints.

I appreciate the Congress' support of the Fisal Year 2005 National Defense Authorization. I believe it is worth quoting from the congressional report language since the rationale coincides with the Department's approach:

The current law [10 USC 2370a] defines biological warfare threats primarily in intelligence terms. This is overly restrictive because intelligence on biological warfare threats is inherently limited due to the ease with which biological warfare programs

can be concealed and dangerous pathogens and toxins can be acquired. The situation is further exacerbated by the rapid advancements in bio-technology that are widely available throughout the world. Additionally, the current law categorizes biological warfare agents by the time period in which they may become threats: near-, mid-, and far-term. For the same reasons that make it difficult to define biological warfare agents in terms of available intelligence, it is difficult to project the time periods during which such agents might become threats. In responding to such threats, more flexibility is needed in the medical components of the biological defense research program.

Key capabilities within the Chemical and Biological Defense Program are structured within the operational elements of Sense, Shape, Shield, and Sustain.

• *Sense* includes advanced remote sensing, standoff detection and identification systems.

• *Shape* includes battlespace management, including modeling and simulation and the communication and decision systems to make appropriate responses and plans.

• *Shield* includes collective and individual protection and preventive medicines, such as vaccines.

• *Sustain* includes capabilities for decontamination and medical diagnostics and therapeutics.

This approach focuses on optimizing materiel solutions for CBRN defense by building a *portfolio of capabilities* that is robust and agile across the spectrum of requirements, including requirements to support homeland security.

Enhancing Countermeasures

As a supplement to the Joint Capabilities Development process, the Secretary of Defense provided direction to enhance the chemical and biological defense posture. The Joint Requirements Office for CBRN Defense and the Office of the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense led a comprehensive study that generated several options for increased investment based on the new requirements and accompanying risk. The study used an analytical methodology to define requirements for each Service and for the total Joint force.

Based on the study findings, senior leaders agreed to increase the investment for WMD countermeasures by $2.1 billion in Fiscal Years 2006–11. This increase includes $800 million in military construction funding included in the Defense Health Program for a recapitalization of the facilities at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The increase also included $1.3 billion for the Chemical and Biological Defense Program, bringing the total chemical and biological defense investment to $9.9 billion over that period. This investment strategy begins with the $1.5 billion Fiscal Year 2006 President's Budget Request. The Chemical and Biological Defense Program increase includes activities to enhance warfighter defense capabilities to include building a new test chamber for non-traditional agents; upgrading test and evaluation facilities; enhancing research and development efforts in areas of agent detection, early warning and battle management, decontamination, collective protection, and medical countermeasures.

The Fiscal Year 2006 President's Budget Submission for the DOD Chemical and Biological Defense Program builds on the strategy and the existing capabilities fielded to protect U.S. forces against CBRN threats and includes the results of the study and biological warfare medical countermeasure initiatives. The Chemical and Biological Defense Program budget provides a balanced investment strategy that includes the procurement of capabilities to protect U.S. forces in the near-term (fiscal year 2006), investment in advanced development to protect U.S. forces in the mid-term (fiscal year 2007–11), and investment in the science and technology base to protect U.S. forces through the far term (fiscal year 20012–19) and beyond. The two primary areas of increased emphasis in this year's budget are the CB Defense Program's test and evaluation infrastructure and novel biodefense initiatives.

This budget is based on technology needs and directions, restructured acquisition programs, and integrated Test & Evaluation (T&E) capabilities to execute these programs. The programs are time and funding sequenced to be executable in terms of having the technologies demonstrated and transitioned in synchronization with the T&E capabilities. Thus, the milestones of the acquisition programs are based on the availability of not only the financial resources, but the technology and T&E resources needed to execute the programs. The full effect of this integrated, executable program structure will begin to be realized in fiscal year 2006.

Medical Countermeasures

In addition to the increase mentioned before, the Fiscal Year 2006 President's Budget submission included an additional $100 million for the CBDP to address bio-

logical warfare medical countermeasure initiatives. Of this funding, approximately 76 percent is applied to science and technology (S&T) efforts and approximately 24 percent is applied to advanced development efforts. These medical countermeasure initiatives will apply transformational approaches which leverage genomics, proteomics and systems biology data exploitation. The focus of these biodefense initiatives is on interrupting the disease cycle before and after exposure, as well as countering bioengineered threats.

The Chemical and Biological Defense Program has made progress in several areas of medical defense. I will briefly describe some recent successes. In 2003, the first successful application of the new "animal efficacy rule" occurred with Food & Drug Administration (FDA) approval of pyridostigmine bromide to increase survival after exposure to soman nerve agent poisoning. Evidence shows that administration of the drug before exposure to soman, together with atropine and pralidoxime given after exposure, increases survival. The FDA agreed that, based on the animal evidence of effectiveness, pyridostigmine bromide is likely to benefit humans exposed to soman. The safety of pyridostigmine bromide has been documented over years of clinical use in the treatment of the neuromuscular disease, *myasthenia gravis.*

In March 2005, a contract award was made for development of a chemical agent bioscavenger for a pre- or post-exposure treatment of nerve agent exposure. This bioscavenger is being developed as a prophylactic regimen to protect the warfighter from incapacitation and death caused by organophosphorus nerve agents.

On the biological side, in early 2005, clinical trails began for a multivalent botulinum vaccine for serotypes A and B, and a plague vaccine; while in July, clinical trials will begin for Venezuelan Equine Encephalitis Vaccine.

Joint Vaccine Acquisition Program

The Joint Project Manager for Chemical Biological Medical Systems is responsible for systems acquisition, production, and deployment of FDA-approved medical countermeasures against chemical and biological agents for the Department of Defense, including the Joint Vaccine Acquisition Program (JVAP).

Near-term (fisacl year 2006–07) biological medical countermeasure goals include transition to advanced development of bacterial (plague), and viral (Venezuelan Equine Encephalitis (VEE)) vaccines.

Mid-term (fiscal year 2008–11) opportunities include advanced development of filovirus and ricin toxin vaccines, potential FDA approval of a reduced dosing schedule for the current anthrax vaccine) and a Botulinum A/B neurotoxin vaccine.

Long-term (fiscal year 2012–20) targets include licensure of all near-term and mid-term vaccine candidates in advanced development to include Eastern and Western Equine Encephalitis (EEE and WEE) and combined filovirus vaccines. Furthermore, the program is investigating several alternatives to hypodermic needles for administration of vaccines, which will greatly reduce the medical logistics burden and cost associated with vaccination, and improve user compliance. Another thrust is to identify effective adjuvants to reduce the time and vaccine dose required for development of effective protective immunity. A strategic thrust is to develop innovative multi-agent vaccines that simultaneously target multiple pathogens through a single immunization series. This effort is supported by the investment the program is making in science and technology.

Major technical challenges in the medical pretreatments capability area are being addressed both within the JVAP as well as in the science and technology base supporting the development and transition of vaccines and related medical countermeasures. These challenges include:

- defining appropriate in vitro and in vivo model systems for investigative purposes,
- determining mechanisms of action of the threat agents as well as their countermeasures,
- identifying appropriate immunogenic protective antigens for vaccine targets,
- stimulating immune responses to small molecules,
- selecting vector systems for recombinant protein vaccines,
- evaluating preliminary safety and efficacy data, determining dose and route of administration, and evaluating process-scale up potential. The development of acceptable surrogate markers of effectiveness is essential to obtain FDA licensure of medical CBD pretreatments, because challenging humans with chemical and biological threat agents to establish vaccine protective efficacy is unethical and prohibited.

Products currently licensed and procured under the JVAP are Anthrax Vaccine Adsorbed (AVA) and Vaccinia Immune Globulin IV, and Dryvax smallpox vaccine. More specifically, JVAP is developing the following vaccines for eventual FDA licensure, listed along with significant program milestones and events. The status of each follows:

• PLAGUE vaccine: Phase 1 clinical trial is being conducted at the University of Kentucky, Lexington, KY. The Phase 1 clinical trial started on January 25, 2005.
• RECOMBINANT BOTULINUM (RBOT) A/B vaccine: Phase 1 clinical trial is being conducted at the University of Kentucky, Lexington, KY. The Phase 1 clinical trial started on August 30, 2004.
• VENEZUELAN EQUINE ENCEPHALITIS (VEE) vaccine: A Phase 1 clinical trial will be conducted at Radiant Research, Austin, TX. The Phase 1 clinical trial is scheduled to start in July 2005.
• VACCINIA IMMUNE GLOBULIN INTRAVENOUS (VIG-IV): VIG-IV was licensed by the FDA. The FDA issued an approval letter to DVC on February 18, 2005 to market Vaccinia Immune Globulin Intravenous (human) (VIG-IV).

Interagency Program Coordination

The DOD Chemical and Biological Defense Program activities are informally coordinated with the Department of Health and Human Services, including the National Institute of Allergy and Infectious Diseases (NIAID), and the Centers for Disease and Control and Prevention. This coordination is evident by the DOD's active participation in the monthly DHHS Risk Management meetings for anthrax, smallpox, and botulinum toxin.

The DynPort Vaccine Company (DVC) is the DOD prime systems contractor for vaccine development. In addition to serving the needs of DOD, NIAID also funds DVC for some collaborative vaccine efforts. These awards included two grants to support the development of a vaccine candidate for botulinum toxin, a grant to support a Phase II trial of a Venezuelan Equine Encephalitis vaccine, and a contract to fund research on a vaccine candidate for tularemia.

It is important to note that some of the medical countermeasures currently being developed through CDC for the national stockpile have their technology basis in programs which originated in DOD. Examples are the next generation anthrax vaccine and cell culture derived smallpox vaccine. As such, DOD and CDC work cooperatively to leverage medical countermeasure programs of mutual interest including the role played by the DVC for such development. Both DOD and CDC have reviewed their programs to ensure there is no funding redundancy.

Management of the development and implementation of national security policies related to CBRN defense activities by multiple agencies of the U.S. Government are coordinated by the joint Homeland Security Council/National Security Council's Policy Coordination Committee for Biodefense. The DOD is represented on this Coordinating Committee.

Medical Countermeasures and Technology Transition—Bridging the "Valley of Death"

There are two rules of thumb that are based in some degree on the historical efforts with the pharmaceutical industry. First, fewer than one in one hundred candidate drugs will receive approval by the FDA for Investigational New Drug (IND) status, and of those, only about one in four will receive approval by the FDA. Second, once a product receives IND approval, it may take 8–10 years and $500–$800 million or more to support the clinical trials and development manufacturing processes to bring a product to market. This does not include the research investment to develop candidate products.

The so-called "Valley Of Death" (VOD) is the time and investment gap between the identification of candidate medical products from the science and technology base and before they are ready for clinical trails.

We are looking at ways to speed up the overall development process for licensure of potential medical countermeasures, which can take 10–20 years. The most promising time savings will probably occur in the initial 2–5 year period during the drug or vaccine candidate discovery phase and prior to the start of clinical trials, the so called VOD. With adequate funding, Good Manufacturing Practices (GMP) manufacturing capabilities, and required biocontainment facilities, the pre-clinical animal safety and toxicology testing might also be accelerated.

FDA has a "fast track" status for review of clinical trials data, but the required structure and time lines for clinical trials, and for product approval are not promising areas where significant shortening of the licensure process can occur.

The Department of Defense's approach is a multi-pronged approach that includes a multi-disciplinary scientific and technical approach, potential changes or improvements in acquisition regulations, cooperative with industry and academia to facilitate venture investments, and continued investment in the medical countermeasures within the DOD Chemical and Biological Defense Program. Ultimately, some of the solution may lie outside the scope of the authorities of our Department and will require interagency cooperation.

BioShield Act

A critical aspect of interagency coordination is DOD support for Project BioShield. As Dr. Klein testified before the House Government Reform Committee in April 2003, it was the intention of the Department of Defense to support this effort. Our intentions have been put into action since that time. The first product that DOD may be able to transition to the Department of Health and Human Services (DHHS) under Project BioShield is the plasma derived bioscavenger. The DOD has awarded an initial contract through Phase I clinical trials, and upon completion, it may be eligible for procurement by the Department of Health and Human Services under Project BioShield. It is important to note that military and civilian capabilities and concept of use for medical countermeasures do not always coincide. Military capabilities requirements generally focus on pre-exposure prophylaxis for a smaller, more defined population, while civilian requirements focus on post-exposure prophylaxis or treatment for a larger, more diverse population. The route of administration requirement for a product may be very different.

DOD's role in BioShield provides potential authorities and tools to streamline the acquisition of needed WMD medical countermeasures for the government. DOD's role in BioShield allows it to: a) leverage its military requirements for medical countermeasures with Department of Homeland Security and the Department of Health and Human Services resources for research, development, and procurement activities; b) continue to produce viable medical product candidates from the DOD research tech base; c) and maintain the unique DOD intramural medical biodefense program.

Thank you for the opportunity to address these issues. I will try to address any additional concerns or questions the subcommittee may have.

SUMMARY OF TESTIMONY OF COLONEL JOSEPH PALMA, M.D., USAF

Chairman Burr, Senator Kennedy and members of the subcommittee: I am honored to appear before your subcommittee. I am Colonel Joseph Palma, the Medical Director within the Office of the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense. I will provide information on Department of Defense efforts to develop promising new medical countermeasures to chemical, biological, radiological, and nuclear (CBRN) threats. I will also address concerns related to the transition of candidate technologies to the point where BioShield Act authorities may be used to fund the procurement. I will also share my thoughts on the perceived "Valley of Death" related to drug development. Following my comments, I welcome any questions the subcommittee may have and I will do my best to answer them.

The major topic areas that I will discuss are:

1. DOD Chemical and Biological Defense Program—From Strategy to Programs.
2. Enhancing Countermeasures.
3. Medical Countermeasures.
4. Interagency Program Coordination.
5. BioShield Act.
6. Medical Countermeasures and Technology Transition—Bridging the "Valley of Death."

Senator BURR. You all did a great job of summing up what we currently do. I am going to ask a different question. I am going to come to you, Dr. Raub. Would you consider the participation in the efforts to create these countermeasures by companies is robust?

Mr. RAUB. I believe it is robust, but needs to be much more so in terms of the challenges that are ahead of us.

Senator BURR. What percentage of those companies that are out there today are actively pursuing countermeasures that might be beneficial to us as a percentage of the overall work?

Mr. RAUB. I don't have that figure, sir.

Senator BURR. I guess my question is, we lack an obvious participation by big pharma. Now, that is for you to tell me whether it is important and for me to listen to you. But as one charged with putting together the plan, but question is, why aren't they involved? What is it in the system that is not enticing to them? Do you have any feel for that?

Mr. RAUB. From my perspective, Senator, many factors play into that. I can't say in every instance which are the principal determinant ones. But again, by definition, we are dealing with current or potential products for which there is little or no commercial market beyond the interest of the Federal Government in the acquisition for biodefense. Therefore, for many companies, certainly the larger companies, they have many alternative business opportunities to pursue and initiatives in this area must be weighed against them.

One of the early concerns that leaders of industry expressed to us has been addressed by the BioShield legislation, and that is many of the companies told us years ago they were concerned about the vagaries of annual appropriation processes and were concerned that upon making commitments for a multiyear endeavor but being dependent on the year-by-year decisions on appropriations, that was more uncertainty than they were comfortable addressing. The special reserve fund for BioShield addresses that question head-on by providing that large up-front appropriation and enabling us to enter into acquisitions when we have the sufficient threshold of knowledge and technology to be able to say with assurance the funds are here, and to the extent that the company can deliver on it, it knows those funds will be available.

I think those are just two of what I am sure are many other considerations.

Senator BURR. Dr. Palma, can you describe for all of us the requirements that DOD uses to determine the kind of countermeasures that you invest in?

Dr. PALMA. Yes, sir. We have a very structured requirements process that is driven by the combatant commander's understanding of what their vulnerabilities are. They look at the threats, but not in the context of, I have anthrax to worry about, but what the context of the war is. And with that, they come up with a requirement to have protective countermeasures against A, B, C, D, whatever the issues are.

We then subsequently incorporate that into the operational process and the operational planning through the Joint Staff analysis process and out of that comes a series of requirements that then our office has to find a way to source, resource, and create countermeasures, again. That is done not just by our office alone. It is obviously done with the entire community as we develop the most promising sort of—we characterize the most promising answers to the shortfalls that the Joint Staff identifies or the requirements that the Joint Staff identifies.

Senator BURR. You spend—the DOD spends a good chunk of money on countermeasures and the research and development that goes into it. In your estimation, how much of that is directed toward the latter stages of development—animal efficacy studies, human safety studies, that is vitally needed for the FDA licensure?

Dr. PALMA. It depends on how you actually frame that. We do some of that—we do all of the FDA stuff starting at the very beginning, so some of the resources that are expended in basic science, for example, the basic science and the exploratory sciences, actually, once we start thinking about having a candidate, we start having conversations with the FDA early. So how much funding

specifically is expended in that from the overall budget, I can tell you how much we spend in the research, development, testing, and evaluation, which includes all of that. In fiscal year 2006, we spent about $250 million—in fiscal year 2005, rather. In fiscal year 2006, we plan to spend about $338 million.

But that doesn't tell the whole story because a lot of that includes the actual testing, the actual lab bench, the actual salaries, the actual infrastructure cost that we need to support, and with that money, we have to do a lot of countermeasure development.

Senator BURR. Dr. Heilman, I noticed as I read through testimony that your division is where the action in terms of conducting the research on bioterrorism pathogens of concern and emerging diseases. Can you describe to me how your division is addressing the threat that most believe exists from genetically engineered pathogens?

Dr. HEILMAN. Yes. There are three general approaches that we are taking that are corresponding to our near, intermediate, and far-term concerns. The near-term issue we are focusing on are engineered threats that are natural threats, and what I mean by that are antimicrobial resistants. We know those things are out there and we know that they present a threat, an important near-term threat. In that particular case, we are spending about over $170, $180 million per year in research in those areas.

The research includes the discovery of new drugs, the better diagnostics of antimicrobial resistant specimens, but also understanding how we can enlarge upon existing drugs that we have in our armamentaria to perhaps counteract drugs—these pathogens, as well. For example, certain drugs are not licensed for a particular bacteria, but they may indeed be valuable for that bacteria when they are in an antimicrobial resistant form. So we are looking at that possibility.

The second kind of area that we are focusing attention on are things that we do know actually have potential threats. One example that I can give you is that—I am sure you have all heard about the IL-4 insertion in ectromelia. That was a study done in Australia, and raised a concern about perhaps the potential of developing a super-smallpox virus. In that particular case, we have been looking at both the vaccines and some of the new drugs that we have been working with companies on in terms of their abilities to counteract that, and actually, brand new data that occurred actually last week has shown that a combination of two drugs that we had been working on actually completely cured ectromelia IL-4 insertions in mice. So we are very pleased about that.

I think the long-term issue is really trying to figure out if there are other approaches that we could be taking to figure out how to address unknown threats, and one of the approaches that we are taking, instead of thinking of the pathogen, we are thinking of how to really harness what we know about the body and the immune response to the body.

For example, the innate immune response is one of the first ports of defense. It immediately is triggered when something unusual occurs. Can we harness the information there to be able to figure out how it should really focus new drugs and new attention on how to

boost this innate immune response? So that is the other approach that we are trying to take at this time.

Senator BURR. I noted that your institute recently announced and created a new position and hired a new person, Dr. Kurilla, am I——

Dr. HEILMAN. He is right here.

Senator BURR. OK—whose primary role will be to provide overall institute coordination for advanced product development of medical countermeasures against bioterror threats. Does this position address that Valley of Death?

Dr. HEILMAN. This position is really intended to figure out how to harness our best approaches to try to do our part of the biodefense acquisition and development process, and what I mean by that, we really focus our attention at the very beginning, on basic research, on the way that basic research can be applied, and then advanced development as defined by Dr. Raub up to the point of really Phase I early to Phase II studies. So Michael's job is really focusing on how best to do that within our resources.

Senator BURR. Does he have responsibility in this position, or will he, to formally coordinate efforts with DOD and DHS?

Dr. HEILMAN. Absolutely. Forgive me for not adding that, but absolutely. He is our principal point of contact, especially with the DHHS and DOD. He has been on the road quite a bit making sure that everybody knows that.

Senator BURR. How did that exist before this position, or did it?

Dr. HEILMAN. Here.

Senator BURR. OK. So you just had one more duty?

Dr. HEILMAN. You have got it.

Senator BURR. Dr. Raub, in your written testimony, you noted that a drug, and I would assume a vaccine entering Phase I trials has only an eight percent chance of reaching the market. At what point do you know that a particular drug is a winner?

Mr. RAUB. The easy answer, sir, is when it is approved or licensed. [Laughter.]

In shaping the acquisitions for the BioShield Special Reserve Fund, in many ways, the overall determinant is do we have something that is licensable or approvable within an 8-year period. Now, that is necessarily subject to scientific and technical expert judgment about whether the conditions are met, but the types of things that the FDA would consider in making its decisions about licensure or approval would be is it safe, is it effective, can it be manufactured in reproducible ways, is it stable, a whole other set of considerations.

And to be able to predict whether that can be achieved, one has to have information about such things as the toxicology of the agent, how the body deals with it, the so-called pharmacokinetics. You need to have information about the efficacy in animals, because for these agents, it would be unethical to experiment upon humans, and especially if they are not naturally occurring. We don't get that information, either, Phase I clinical trials, as Dr. Heilman indicated, and manufacturing scale-up work. Something made at the benchtop successful may founder when one tries to produce it on a commercial scale. So it is all of that kind of infor-

mation that is subject to an expert analysis that leads to this decision, is this licensable or approvable most likely in that period?

So far, so good, we believe in our judgments, but these are judgments and only history is going to tell exactly how sure one can be with respect to is this a winner.

Senator BURR. Dr. Vitko, once you provide that threat and risk assessment, do you actually participate in drafting the requirements and ultimately those requirements are issued by HHS?

Mr. VITKO. We participate in the process that generates those requirements. HHS formalizes them. The process that occurs after we do a threat assessment and then a threat determination is there is an interagency group called the Weapons of Mass Destruction Medical Countermeasures Subcommittee, which is co-chaired by HHS, DHS, and DOD, and exists under the aegis of the Office of Science and Technology Policy.

That committee meets and assesses the consequences of such a threat. That is, are there currently available medical countermeasures that address that threat? If not, are there things in the pipeline that do? And if so, it makes recommendations amongst the various options on what they consider the most prudent path to pursue, and those options then are forwarded to HHS and HHS finalizes those requirements and seeks approval from OMB to then go and issue an RFP for those medical countermeasures.

Senator BURR. Can I ask you to be a little more specific on the level of participation that you have?

Mr. VITKO. Yes. As I said, DHS co-chairs that committee with the other agencies. Typically, what we do in our role there is, first of all, we actually participate in the studies that look at the plausible scenarios. How many people might be exposed? Can this occur in one city or multiple cities? What are the other associated effects with this that might affect distribution of medical supplies, that is the timing and where they could be distributed? So we participate in that as a co-equal and then we certainly co-chair the process to then have an equal vote with everybody else on the decisions of which options to look for.

Senator BURR. I am going to ask one more question and then I am going to turn to my colleague, Senator Hatch. Are we wrong to be so concerned about this area we have all referred to as the Valley of Death? Is this something that we should not be focused on? Is it not a problem, or is it?

Mr. RAUB. I can start, Mr. Chairman. My colleagues, I expect, will want to comment, as well. I believe it is appropriate for the committee, as well as the agencies, to focus on it. In my own perspective, the Valley of Death is not an inevitable part of the landscape for every product, and I have given a couple of examples where things have passed smoothly from the early stages of research to acquisition.

But some products may well encounter this, either by the nature of the product, some scientific and technical considerations, or the circumstances of the time, and what I mean by the circumstances of the time, it may be the competition for other funding, whether it is NIH funding or DOD funding or venture capital. There may be other more attractive opportunities at that point, and some individual products may very well encounter this dearth of means to

be able to pursue questions, whether it is manufacturing scale-up, toxicology, Phase I trials, all those things that are necessary to put it within reach for a BioShield acquisition. So we believe the committee is quite properly focused on this as an important issue for all of us.

Senator BURR. Anyone else?

Dr. PALMA. Yes. I would agree with that. I think it is essential, and I don't think I would find anyone here that would disagree with me. I don't think John would, either. I think it is essential that the Nation recognize that there is a risk in the development of biodefense products that is unique and that resourcing that risk appropriately, and by that, I mean people, infrastructure, intellectual capital, and continuous funding for those efforts that are necessary to fund.

I think those decisions need to be informed by an understanding of what is understood to be the Valley of Death, and I would define that a little bit more broadly, because I think that all products go through that kind of challenge. But understanding those challenges and resourcing them appropriately is essential if we are going to have success in addressing all of the challenge of biodefense that we really face. It is not like a Manhattan project, because that was about nuclear physics. This is about the diversity of biology and it is a much more complicated problem.

Senator BURR. Senator Hatch.

Senator HATCH. Welcome to all of you. We appreciate the work that you do for our country and the protection of our citizens.

Dr. Vitko, I want to thank you for your testimony and for sharing with us the DHS's efforts in this area. Now, I personally am pleased to hear you call for the infrastructure to support rapid research, development, test and evaluation of new medical countermeasures, as this is exactly what my colleagues, Senator Lieberman and others, Senator Brownback included, and I have attempted to do with our BioShield II legislation.

In your testimony you State that the Science and Technology Directorate helps to provide an end to understanding of an integrated biodefense strategy. In contrast, there have been complaints by some biotech companies that the lack of cross-agency requirements or standards for some of these products creates obstacles for their work in this area. Now, do you feel that there is currently a widely known, acceptable, and effective integrated biodefense strategy that spans all governmental agencies?

Mr. VITKO. I think the short answer is at the top level, yes. The President's Biodefense for the 21st Century called out the key elements of such a strategy, assigned agency responsibility, and in the classified version of science-specific taskings, the agencies in it.

At the next level of specific milestones and steps along those, they are at various levels of development, some more advanced and complete than others.

Senator HATCH. Does anybody else care to comment about that?

[No response.]

Senator HATCH. OK. Dr. Raub, thanks for your testimony. You mentioned that our smallpox vaccine stockpile now contains enough vaccine for every person in America. Do we also have the infrastructure necessary to distribute those doses?

Mr. RAUB. We believe we do have the basic infrastructure. Part of the smallpox immunization campaign over a year ago was involved not just in encouraging health care workers to be vaccinated, but to working with public health departments to build the basic infrastructure for delivering vaccinations.

In addition, in a related area, namely our concern about the anthrax threat, we have been leading an effort called the Cities Readiness Initiative, which focuses on 21 major metropolitan areas in the country, building the local infrastructure for the rapid distribution of antibiotics. Now, vaccines are a bit more difficult to administer than giving out pills, but there is more similarity than difference with respect to the kinds of temporary clinics and logistics and other aspects of that dispensing.

So we are leveraging the experience on the smallpox vaccination specifically with this larger effort on Cities Readiness and we will continue to do that. It is a major feature in the 2005 and 2006 budgets for HHS, and we feel confident that that is strong now and will get better as we work with our municipal and State colleagues.

Senator HATCH. Thank you. Dr. Palma, thank you for providing the Department of Defense viewpoint. It was very interesting to hear about some of your successes in that area. But what aspects of the Department of Defense's approach to procurement are the most or least suited or suitable to adaptation into civilian markets?

Dr. PALMA. Senator Hatch, there are—we have an ongoing relationship with HHS. We meet on a monthly basis on common product, common interest, and we are on the verge of signing an interagency agreement with them to actually have a tighter collaboration. So from a process standpoint, we both participate and try to share the workload and identify those things where we have commonalities of interest to pursue them in a common sort of way.

Several of our countermeasures, and many of the countermeasures that are currently in development at DHHS certainly have their roots in DOD work that has been going on at USAMRA and places like that for many, many years. So of which products themselves lend themselves to civilian use, many of them do.

Many of those products were not developed past IND and really were not fully licensed at the time that HHS got them, so they are spending some money to do that where we don't have it. And where we have it, we are spending some money to do that.

So I think it is fair to say that in many, many cases, the needs are similar, but in some cases, the operational imperatives are different and we then have to pursue our own efforts separately because it is unfair to ask the other agencies to pay for that.

Senator HATCH. I appreciate all four of you and what you have been able to do for us and what you are trying to do and for the efforts that you are putting forth. These are all very, very difficult problems. I haven't asked you, Dr. Heilman, about your agency, but I know what you are doing and it is very, very important for the protection of all people in our country.

We need advice up here as to what we should do better, so any time you feel like sending it up here, we would love to look at it and see what we can do to help you.

I certainly appreciate our chairman here. He has been really working hard on this, in this area, and I think he deserves a lot

of credit for making sure that we are up to speed on a lot of these issues that are so important in this world epic that we are going through. Thank you. I appreciate it, Mr. Chairman.

Senator BURR. Thanks, Senator Hatch.

I am going to come back to you, Dr. Raub. If I understood what you said, you said that the public health infrastructure was sufficient to be able to handle a mass inoculation were we to need that.

Mr. RAUB. I believe I said it was strong, sir. I don't think I said it was sufficient, and the reason we have that initiative is to work to achieve that sufficiency. We have strong capabilities, not strong enough for some of the challenges that we can envision, which is why we are making a special push on it.

Senator BURR. I think I might agree with you if we were geographically cherry picking a map of the United States of America, but I think the challenge for us as we put together legislation is to be blind geographically as to where something may happen. Therefore, the plan has to have the ability to meet that need in any corner of a very large land mass. I commend you for the progress that we have made, all of the departments.

I think that, personally, one of the areas that I see that may deviate from where we initially thought the scope of this bill would be is to focus very heavily on the public health infrastructure in this country, possibly to redefine the role of public health for the future. I look forward to working with HHS as we explore whether we need to go there, and if we do, what the changes are that we might need to make legislatively to enable that to happen.

You did allude in your testimony, and Senator Hatch also brought it up, that we have procured enough smallpox vaccine for every American. I think you have committed to buy anthrax vaccines for the stockpile, and NIH has recently announced grant awards to expedite research on a number of dangerous pathogens.

I want to come back to the procurement process, because I think it is likely that there is a process in place that we understand very well at HHS and the outside world doesn't understand one bit how it works. I have heard from several company executives that they don't know the specific requirements for countermeasures that are needed, and more importantly, they don't have any clue what the size of the intended government purchase would be. Can you comment on that at all?

Mr. RAUB. Yes, sir. I am actually surprised to hear that, because our requests for proposals are highly specific documents. I mentioned earlier that leaders of industry had encouraged us to deal with the stability of funding question. What they also encouraged in those same meetings were two other things related to this. One is when we went out with a request for proposals, for this to be scientifically and technologically well-grounded, including manufacturing capability, not some fancy of a bureaucrat. They wanted something that was evidence-based and could be done.

Second, they wanted us to be specific as to how many doses, in what form, by when, and I believe our requests for proposals meet that.

Where I believe some of the criticism may be emerging is not so much the specificity of our requirements, but whether various opportunities reach that threshold. We have received some criticism,

for example, of hoping that we would issue requests for proposals in areas where, in our judgment, the underlying evidence was inadequate. We didn't see even Phase I clinical trial information. We didn't see information on manufacturing scale-up and these other elements that are part of that decision, is there a licensable or approvable product here in 8 years? And I think we have been criticized for where we have made that determination. But I don't believe a criticism based on any vagary or ambiguity of the RFP would hold up.

We continue to try very hard through our website, through our staff's participation in conferences, for everybody to understand the strengths and the limitations of BioShield as the law defines it, and I am sure there are communication issues that we can do better on and we can resolve. It is very much in our interest to have a clear understanding and a good interaction with the industry, large and small, as well as our academic colleagues. So we will certainly take to heart what you have expressed, but I believe we are super-specific in those RFPs.

Senator BURR. Clearly, it is in all of our interest that we perfect it if, in fact, it is flawed at any point.

I want to thank this panel for your willingness to be here, for the expertise that you have brought. I think it is safe to say that Senator Hatch and Senator Lieberman, Senator Gregg, Senator Frist, Senator Kennedy, there are some passionate members of this committee on this issue, and probably more so than I have found on most issues that come through this fine institution. There are some differences and the challenge of the subcommittee is to sort through the proposals that might lead one to address liability, and if we solve liability, we have now a robust participation in the program, others that believe it is patent extension and that if we solve that, it is robust participation in the program, or questions that we have raised today about the unclarity that exists in procurement might, if cleared up, generate robust participation in the program.

Over time, we will have the opportunity to try to figure out what the balance is of those and other things and we look forward to working with each of you on how we achieve that. Thank you very much.

Senator BURR. I would call up the second panel at this time. Let me take this opportunity to welcome our second panel. I have made the introductions in my opening statement.

At this time, let me recognize Mr. Timmins for his opening statement.

STATEMENTS OF ALAN P. TIMMINS, PRESIDENT AND CHIEF OPERATING OFFICER, AVI BIOPHARMA, INC., PORTLAND, OR; RICHARD FROTHINGHAM, M.D., ASSOCIATE PROFESSOR OF MEDICINE, DUKE UNIVERSITY MEDICAL CENTER, AND STAFF PHYSICIAN, VETERANS AFFAIRS MEDICAL CENTER, DURHAM, NC; DAVID P. WRIGHT, PRESIDENT AND CHIEF EXECUTIVE OFFICER, PHARMATHENE, INC., ANNAPOLIS, MD; PHILLIP K. RUSSELL, M.D., U.S. ARMY MAJOR GENERAL, RETIRED; AND SCOTT MAGIDS, DIRECTOR, TECHNOLOGY ADVANCEMENT PROGRAM, UNIVERSITY OF MARYLAND

Mr. TIMMINS. My name is Alan Timmins and I am the president and chief operating officer of AVI BioPharma, Inc. AVI is a biotechnology company that was founded in 1980 out in Oregon, and it was founded under the premise that the gene could be the target for drug intervention. Since that time, we have made a distinctive proprietary technology that, in fact, through 11 clinical trials and over 300 patients treated has not had a single adverse event in clinical trials.

In reference to biodefense, we are currently working on programs in Ebola, Marburg, influenza viruses, as well as the anthrax and ricin toxins.

Our technology is particularly applicable in the rapid response setting, as perhaps best illustrated by an accident that occurred about 16 months ago at USAMRIID, where a researcher suffered a needle stick while working with the deadly virus Ebola. We got a call from the USAMRIID researchers, who identified Ebola targets. We synthesized drugs. We assisted USAMRIID in getting an emergency IND from the FDA and we delivered drug for use at USAMRIID all within a 5-day period of time. That is unheard of in the world of pharmaceuticals.

Happily, that researcher never became symptomatic, so after 21 days in isolation, the researcher was released. The drug, however, was used later under a cooperative research and development agreement at USAMRIID and was useful in forwarding the research in mice.

We have ongoing programs now in several infectious diseases and toxins and we believe that we can address fully at least 75 percent of the agents identified on the CDC's list of bioterror threats. Also importantly, though, our experience over the past 16 months puts us in a position where we believe that we could also address specifically engineered threats that are made to be used as bioterror agents.

As you might imagine, over these 16 months, we have come across a number of challenges, scientific and research challenges we have met and will continue to meet in the future. What we haven't been able to meet and what we can't figure out are the bureaucratic confusion, or as you call them in your opening statement, the gaps that exist between BioShield and the real world. I outline for you, Senator, three of those gaps.

The first is a funding gap that occurs between the time of proof of scientific principle and the time when a product is ready to be considered for BioShield. We as a small company look to the capital markets for our funding. Specifically, we raise money through sales of stock. We don't have any sales, and so we can't contribute reve-

nues to government research. The money that we get in the capital markets is operating capital. It is not for government seed funding.

Therefore, the possibility exists that a promising product, for example, our Ebola product, could die on the vine simply because, while it has been proven scientifically, it is not far enough along for BioShield. That is a specific example. We have been told by DARPA that we are too far along for funding from them on our Ebola product, but BioShield has said we are not yet far enough along for them to consider it as a product acquisition. I believe that the way BioShield is structured would, though, allow for such funding. So I think that the emphasis needs to be made there.

The second gap that we have identified, I will call an implementation gap. Senator, I will tell you that the perception of the process of BioShield, of BioShield acquisition, is a complete black box. It is not understood by industry. It is not understood by the street. Companies shy away from participating in BioShield because it is considered to be too difficult or perhaps too mystery-endowed to be worthwhile for a company to risk its assets moving forward with a BioShield product.

An example of that, HHS is thought to require an IND, or an Investigative New Drug filing with the FDA before they will allow a company to bid on a BioShield contract. In fact, if you read the legislation, S. 975, or you talk to the people that were critical in writing it, folks from Senator Lieberman's office, for example, they will tell you that that is not the case. It is not in the legislation, nor was it ever considered to be part of the legislation. So there is a gap in understanding of what it takes to be successful, a clear path to success in Project BioShield.

The third gap that I will tell you about is what I call an incentive gap. The difference between the risks of performing or working to perform under BioShield and the rewards of being successful are too great. That is why in answer to your question for the first panel about why you don't see big pharma there, it is because of that. The risks are considered to be too great because the rewards are not enough.

How do you address that? I think a good start to that would be to adopt a legislation called BioShield II and the related legislation. That way, you can provide the tax incentives, patent incentives, liability protection, and the intellectual property protection that those Acts have in place.

So in summary, I have outlined a number of gaps that exist. I think that it is a large issue that needs the focus of the Senate, certainly of committees like this one. I think that by being proactive, I think that is the necessary step because I think what this subcommittee and all the people in here would agree is that you don't want to suffer the terrible potential consequences and costs of waiting and being reactive to a bioterror event.

Thanks. I look forward to your questions.

Senator BURR. Thank you, Mr. Timmins.

[The prepared statement of Mr. Timmins follows:]

PREPARED STATEMENT OF ALAN P. TIMMINS

Introduction

Chairman Burr, Senator Kennedy, and members of the subcommittee: My name is Alan Timmins and I am the president and chief operating officer of AVI BioPharma, Inc. AVI is a biotechnology company based in Oregon, which was founded in 1980 on the premise that genes could be the target for drug intervention. AVI has developed a proprietary third-generation technology, distinct from that of any of our peers, which we focus on unmet medical needs. We have conducted 11 human clinical trials with this technology in over 300 patients and shown our technology to be safe and efficacious in cardiovascular disease and drug metabolism.

AVI is currently pursuing commercial applications of its technology in infectious disease, cardiovascular disease, and cancer. More germane to this hearing, AVI is currently pursuing biodefense and public health applications of its technology against Ebola, Marburg, and influenza viruses, and ricin and anthrax toxins.

Applicability of Technology

AVI's proprietary technology is particularly well-suited to rapid response in biodefense and public health settings. This was perhaps best illustrated by an incident approximately 16 months ago at the US Army Medical Research Institute of Infection Disease (USAMRIID) located within Fort Detrick, MD. There, a researcher experienced an accidental needle stick from a syringe while working with Ebola Zaire virus. Ebola is a very lethal virus, historically fatal in more than 80 percent of infected individuals. Upon receiving a call from scientists at USAMRIID requesting our assistance, AVI found relevant genetic sequences, synthesized two drugs, assisted USAMRIID in securing an emergency IND from the FDA, and delivered those drugs to USAMRIID within 5 days of the original request. Fortunately, the researcher showed no Ebola symptoms and was released, after 21 days of isolation, without requiring drug intervention. The same drugs delivered to USAMRIID, however, were successfully put to use in ongoing research at USAMRIID under a Collaborative Research and Development Agreement (CRADA) between AVI and USAMRIID.

AVI has ongoing programs with outside investigators in other infectious disease and toxin areas including efforts in Marburg, Dengue, Rift Valley Fever, Crimean Congo Fever, Ricin, E coli, Yellow Fever, influenza, Hantaan virus, and SARS. Clearly, all of these diseases or infectious agents are considered to be potential bioterror threats. Specific successes have been achieved in collaboration with government scientists, primarily from USAMRIID, in programs targeting Ebola, Marburg, ricin, anthrax, dengue, and influenza.

In addition to efforts in these areas, we believe that we are able to currently effectively address more than 75 percent of the viruses on the CDC's list of bioterror agents. Further, the lessons learned from studies involving such an array of viruses to date offer the potential to create drugs for rapid response to engineered viruses designed as bioterrorism agents.

Challenges to Biodefense Implementation

As you might imagine, we have encountered numerous challenges along the way as we have pressed forward with our biodefense efforts over the last 16 months. The most daunting challenges we have faced in this endeavor are not in the research or medical areas, as we have met those challenges in the past, and we will continue to surmount them in the future. The most daunting challenges that we have faced, and cannot solve, are those of bureaucratic confusion. There are three main areas of bureaucratic confusion, or gaps, that I will briefly outline.

First, there is a funding gap for smaller companies between the point of reaching scientific proof of principle and the point of having a product ready for Project BioShield consideration. As a small company with limited resources, we must access the capital markets for operating funds. These funds are provided by our investors as risk capital, not as seed capital for government research. Because we do not yet have sales, we have no alternative funding mechanisms for government directed research, and, apparently such funding mechanisms do not readily exist within the government. As a specific example, in our case, we have been told that we are "too far along" for funding opportunities via DARPA or NIH, but not yet "far enough along" for BioShield. Thus, promising biodefense solutions that have no commercial markets, but have a high level of biodefense relevance or public health applicability, like our Ebola virus compounds, might simply die on the vine because there is no government funding mechanism to get us to the point where we can provide you a potential BioShield product. In our opinion, it would not be inconsistent with the

overall approach of BioShield to provide a funding mechanism to span this gap between proof of principle and BioShield product acceptance.

We believe a second gap exists in the understanding and implementation of BioShield. The award process appears to be a "black box," with no clear pathway to success for interested companies. For example, it appears that HHS is requiring that companies secure an IND (Investigational New Drug filing with the Food and Drug Administration) before bidding on a BioShield contract. In fact, the original BioShield legislation, S. 975, makes it clear that an IND in hand is not a prerequisite to contract bidding, nor was it Congress? intent that it should be. This lack of understanding (or understandability) of the playing field, in our opinion, will drive qualified, yet frustrated, companies away from participation in the BioShield effort. Coupled with the funding gap described above, a significant barrier to participation in Project BioShield evolves. Clearly, the losers in each scenario taken separately, and both scenarios combined, are the American people, and whether that loss occurs in biodefense versus in public health is irrelevant.

The third, and perhaps the greatest gap which exists with regard to BioShield is the incentive gap between the risks and rewards for companies considering participation in biodefense. Specifically, the potential rewards which could accrue to a company which successfully bids on, is awarded, and completes a BioShield contract, are not enough to motivate an appropriate number of large and small biotechnology and pharmaceutical companies to participate. The risks of participation are considered too great by most companies due to the gaps described above. These risks could be more than adequately addressed by the proposed BioShield II and related legislation. That legislation, as currently proposed, would offer tax incentives, patent incentives, and liability and intellectual property protection. All of these provisions would be seen to have admittedly different relative values, dependent upon the company considering them; but, in the aggregate, all would be seen as having significant value, and perhaps be the motivating factor which would encourage more companies to actively seek to participate in BioShield.

Conclusion

We believe that the items addressed in the above testimony represent major hurdles for this country to overcome in its desire for a much-needed system of biodefense. Solutions are, however, available. To summarize: first, a system of financial support for smaller companies must be defined and funded to span the gap experienced by small companies between proof of scientific principle and contract consideration in BioShield, particularly for those compounds which have only biodefense or public health viability. Second, the BioShield process, as enacted by Congress, must become more transparent, interpretable, and understandable, thereby becoming more efficient and effective in achieving the goal of biodefense. Finally, BioShield II should be enacted to provide several important protections to companies providing essential biodefense tools for the best interests of the country. These solutions, taken together, will awaken and direct the entrepreneurial spirit of the biotechnology and pharmaceutical industries toward genuine progress in biodefense. By being proactive here, we as a nation can avoid the potential terrible outcomes and costs of merely being only reactive in a biodefense emergency.

Senator BURR. Dr. Frothingham.

Dr. FROTHINGHAM. Good afternoon. I want to first thank Senator Burr and Dr. Cadlick for the invitation to testify today. I consider this to be a genuine privilege.

Academic researchers like myself generate a lot of ideas, including ideas for new drugs, new vaccines. This is what we do best. However, we are not funded or equipped to carry out the developmental studies to initiate human trials and bring new products to market. This Valley of Death that others have spoken of refers to this gulf between the research lab and the clinical trial that a novel therapy must cross over, and as we have heard, most candidate drugs never make it. Dr. Palma estimated one in 100.

Today, I will discuss the Regional Center of Excellence model as a means to overcome the Valley of Death for drug development and I will provide some specific examples from our own regional center with particular relevance to biodefense.

In 2003, the NIH, and particularly the NIAID, funded eight Regional Centers of Excellence in emerging infections and biodefense. I will refer to these as RCEs, Regional Centers of Excellence. The goal of the RCEs is to bring together university researchers to develop new drugs, vaccines, and diagnostics to protect society from biological threats. These threats may involve natural emerging infections, such as SARS, or the intentional spread of germs, such as the distribution of anthrax spores in the U.S. mail.

Development of new drugs and vaccines is a challenging mandate for the RCEs. As I mentioned, universities are not funded at the level of the pharmaceutical companies that normally bring drugs to market. Also, many of the target germs for biodefense research are uncommon infections and few companies are interested in spending money to develop a new treatment unless there is a clear market and a buyer. So the Valley of Death for biodefense can be especially deep.

The RCEs, Regional Centers of Excellence, are working to overcome the Valley of Death in three ways. First, by creating synergy that taps the resources of multiple academic institutions. Second, by creating a virtual R&D company within the university setting. And third, by developing broadly applicable platform technologies.

First, the RCEs are able to tap into multiple Academic Institutions of Excellence. Duke is the lead institution in the Southeast Regional Center, or SERCEB. The SERCEB includes six members institutions, Duke, our arch rival UNC-Chapel Hill, Emory, the University of Alabama at Birmingham, Vanderbilt, and the University of Florida, as well as 16 affiliate members. Our first job as an RCE is to create functional teams across institutions that will bring creativity and intellect to the problems of drug vaccine and diagnostic development.

As an example, we need oral drugs to treat smallpox. Promising candidates have been developed by a biotech company in North Carolina. The SERCEB brought this company together with academic RCE investigators at the University of Alabama, again, part of the RCE, who were able to quickly test them on animal models. A candidate drug is now ready for human trials, hopefully by the fall of 2005.

Second, the RCEs accelerate the process of drug and vaccine development by harnessing the resources of multiple universities to the structure of an RCE, forming what we call a virtual R&D company within the academic setting. This is a combination between the goal-oriented organization, the RCE, with the academic resources of the universities. We have created a new model for product development.

Two examples of this. An investigator at Emory discovered that an FDA-approved cancer drug also inhibits poxviruses. This group of viruses includes smallpox. The SERCEB immediately funded animal trials to confirm this discovery, using the flexibility that we have in the Research Center of Excellence. We then brought the investigator, the NIH, and a drug company together to form a product development team.

Similarly, a Duke lab discovered a new way that HIV may escape the human immune system. Some of the best antibodies against HIV turn out to also react against normal human tissue. This anti-

self antibody response may activate defensive mechanisms in the human body, shutting down the very responses that are needed to fight HIV.

Third, the RCEs are collaborating to evaluate broadly applicable technologies for vaccines and drug development. We call these platform technologies. The RCEs hope to speed the tempo of platform development by drawing together multiple universities and companies.

As an example, many vaccine delivery systems have been described by biotech companies or academic researchers, and typically, each researcher or company will focus on one or two systems. The SERCEB is conducting a major study to compare side-by-side the effectiveness of many different vaccine delivery systems to identify the best technologies for biodefense vaccine. The RCE unites the efforts of multiple participants to generate this type of unique comparative data.

I want to thank you for the opportunity to share my enthusiasm for the Research Center of Excellence model and I will be happy to take questions now or after the presentations.

Senator BURR. Dr. Frothingham, thank you. As a Wake Forest graduate, it is an extension of my generosity to have a Duke or a Carolina— [Laughter.] No, competition is alive and well in the ACC and Washington served as a wonderful host of our basketball tournament this year, as you well know. The one thing that was evident was that the normal Duke team was not there, but I am sure they will return very soon.

Dr. FROTHINGHAM. My daughter will be entering your institution this fall.

Senator BURR. Your daughter?

Dr. FROTHINGHAM. Yes.

Senator BURR. Good. [Laughter.] As time goes on, families learn. [Laughter.]

[The prepared statement of Dr. Frothingham follows:]

PREPARED STATEMENT OF RICHARD FROTHINGHAM, M.D.

Introduction

Good afternoon. I want to first thank Senator Burr for the invitation to testify today. I consider this a genuine privilege.

The "Valley of Death" for Drug Development

Academic researchers like myself generate lots of ideas, including ideas for new drugs. This is what we do best. However, we are not funded or equipped to carry out the developmental studies needed to initiate human trials and bring a new product to market. The "Valley of Death" refers to this gulf between research lab and clinical application that a novel therapy must cross over. Most candidate drugs never make it.

Today I will discuss the Regional Center of Excellence model as a means to overcome the Valley of Death for drug development. I will provide examples from our own regional center with particular relevance to biodefense.

Regional Centers of Excellence (RCEs)

In 2003, the NIH funded 8 Regional Centers of Excellence in Emerging Infections and Biodefense. I will refer to these as RCEs. The goal of the RCEs is to bring together talented university researchers to develop new drugs, vaccines, and diagnostics to protect society from biological threats. These threats may include natural emerging infections such as SARS or avian influenza, or the intentional spread of germs such as the distribution of anthrax spores in the US mail.

Development of new drugs and vaccines is a challenging mandate for the RCEs. Universities are not funded at the level of the pharmaceutical companies that nor-

mally develop these products. Also, many of the target germs for biodefense research are uncommon infections. Few companies are interested in spending money to develop a new treatment unless there is a market or a buyer. The Valley of Death for biodefense can be especially deep.

Overcoming the Valley of Death

The RCEs are working to overcome the Valley of Death in three ways: (1) by creating synergy that taps the resources of multiple academic institutions, (2) by building a virtual R&D company within an academic setting, and (3) by developing broadly-applicable platform technologies.

1. Synergy That Taps the Resources of Multiple Academic Institutions

First the RCEs are able to tap into multiple regional academic institutions. Duke is the lead institution in the Southeast Regional Center or SERCEB. The SERCEB includes 6 member institutions (Duke, UNC Chapel Hill, Emory, the University of Alabama at Birmingham, Vanderbilt, and the University of Florida) as well as 16 affiliate members. Our first job as an RCE is to create functional teams across institutions to bring creativity and intellect to the problems of drug, vaccine, and diagnostic development.

As an example, we need oral drugs to treat smallpox. Promising candidates have been developed by a biotech company in North Carolina. The SERCEB brought this company together with RCE investigators at the University of Alabama, who were able to quickly test them in animal models. A candidate drug is now ready for human trials—hopefully by the fall of 2005.

2. A Virtual R&D Company Within an Academic Setting

Second, the RCEs accelerate the process of drug and vaccine development by harnessing the resources of multiple universities to the structure of the RCE, forming what is essentially a "virtual R&D company" within the academic setting. By combining a goal-oriented organization (the RCE) with the extraordinary intellectual and academic resources of research universities, we have created a new model for product development.

Two examples will illustrate the effectiveness of this approach. An investigator at Emory discovered that an FDA-approved cancer drug also inhibits poxviruses. The SERCEB immediately funded animal trials to confirm this discovery. We then brought the investigator, the NIH, and a drug company together to form a product development team.

Similarly a Duke lab discovered a new way that HIV may escape the human immune system. Some of the best antibodies against HIV turn out to also react against normal human tissue. This anti-self antibody response may activate defensive mechanisms in the human body, shutting down the very responses needed to fight HIV.

3. Development of Broadly-Applicable Platform Technologies

Third, the RCEs are evaluating technologies that may be broadly applicable to vaccine or drug development. RCEs hope to speed the tempo of this work by drawing on multiple universities, and by bridging connections with biotech companies, pharmaceutical manufacturers, and the Federal Government.

As an example, many vaccine delivery systems have been described by biotech companies and academic researchers. Typically each researcher focuses on one system. The SERCEB is conducting a major study to compare side-by-side the effectiveness of many different vaccine delivery systems to identify the best technologies for biodefense vaccines. The RCE is uniting the efforts of multiple participants to generate unique comparative data.

Close

Thank you for the opportunity to share my enthusiasm for the RCE model. I will be happy to take questions now or after the other presentations.

ADDITIONAL RESOURCES

What is SERCEB?

The Southeast Regional Center of Excellence in Biodefense and Emerging Infections (SERCEB) is a consortium of academic institutions in the southeast comprised of member schools, Duke University, University of North Carolina-Chapel Hill, Emory University, University of Alabama-Birmingham, Southern Research Institute, Vanderbilt University, and University of Florida-Gainesville.

The SERCEB affiliate members are East Carolina University, Georgia State University, Medical College of Georgia, Medical College of South Carolina, Meharry College, Morehouse College, North Carolina Central University, North Carolina State

University, Tulane National Research Center, University of Alabama at Tuscaloosa, University of Georgia, University of Kentucky, University of Louisville, University of Mississippi, University of South Florida, University of Tennessee-Knoxville, University of Tennessee at Memphis University of South Carolina , Wake Forest University, Winston Salem State University.

The SERCEB government partners are the Centers for Communicable Disease Control (CDC) and the Oak Ridge National Laboratory (ORNL).

The SERCEB is funded by the NIH from September 2003 to March 2008.

See www.serceb.org for detailed information.

IMMUNE SYSTEM SURPRISE ON HIV

FINDING OF UNEXPECTED ANTIBODY RESPONSE COULD POINT TO NEW VACCINE APPROACH, THURSDAY, APRIL 28, 2005

Durham, N.C.—New insights by Duke medical researchers as to how HIV evades the human immune system may offer a new approach for developing HIV vaccines. The findings suggest some HIV vaccines may have failed because they induce a class of antibodies that a patient's own immune system is programmed to destroy.

The Duke team discovered that certain broadly protective antibodies, which recognize and latch onto the HIV protein gp41, resemble antibodies made in autoimmune diseases. In most people, the immune system destroys these types of antibodies to prevent attacks against self.

The Duke study suggests HIV vaccines may have failed in part because certain proteins on HIV's protective outer coat trigger only short-lived, self-reactive antibodies instead of long-lasting, HIV-specific antibodies. The results also imply that during the initial infection stage in humans, HIV may escape destruction by the immune system because these seemingly vulnerable outer coat proteins activate self-reactive antibodies.

"The fundamental problem in all of HIV vaccine research has been that when you inject the envelope of the HIV virus into people or animals, no broadly neutralizing antibodies—those antibodies that kill most HIV strains—are made. This provides a plausible explanation for why broadly protective antibodies have not been made in response to currently tested HIV vaccines," said Barton Haynes, M.D., lead author of the study and director of the Human Vaccine Institute at Duke.

The researchers will report their findings in a forthcoming issue of Science. The results were published online Thursday in Science Express.

The antibody-producing portion of the human immune system is broadly divided into two categories. The first, innate B cell immunity, comprises fast acting but weak antibodies that fight a broad range of pathogens. These antibodies can also attack the body itself, as in autoimmune disorders such as systemic lupus erythematosus. When viruses activate innate B cells, the body destroys the B cells to protect against autoantibodies that could cause autoimmune disease or other harm.

The second immune system category is adaptive B cell immunity, a slower response that creates powerful, pathogen-specific antibodies and provides lasting immunity. The body's normal response to infection is to produce adaptive antibodies that target only the invading virus or other pathogens. Many widely used non-HIV vaccines "train" adaptive antibodies to seek out a unique protein on the protective outer coating of viruses. HIV researchers have attempted to induce broadly neutralizing antibodies—long-lived, HIV-specific antibodies that can kill all or most HIV strains—with a similar vaccine design.

Some broadly neutralizing antibodies have been isolated from HIV-infected humans, although the antibodies are rare, with less than 5 identified. "We know these antibodies can exist, but we have not been able to give a vaccine to people or animals that stimulates the production of these types of antibodies," said Haynes, who has studied HIV vaccines for 15 years.

In their experiments, Haynes and his colleagues demonstrated that some of these rare broadly neutralizing antibodies are actually polyspecific autoantibodies that react with many proteins, including one's own tissues, like the antibodies made by innate B cells. In laboratory tests, the antibodies reacted with multiple types of human molecules, most prominently with a fat molecule caled cardiolipin.

"It appears the most vulnerable spots on the outer coat protein of HIV, to which the most protective antibodies bind, are the target of autoantibodies that also react with normal human tissues and are normally destroyed by the immune system," Haynes said.

Haynes, an AIDS researcher who has also studied autoimmune diseases, began to focus on possible similarities between HIV infection and the biology of

autoimmunity after work on an experimental outer coat vaccine failed to produce broadly neutralizing antibodies in animals.

"Recently, we spent 2 years making an experimental outer coat vaccine candidate that had the correct areas on the outer coat for the good broadly neutralizing antibodies to bind to, and we vaccinated several kinds of animals. In none did we get any of the good antibodies. That frustrating result led me to ask if something was preventing these good antibodies from being made," Haynes said.

"A light went on when I saw that the rare human monoclonal antibodies had physical characteristics very similar to autoantibodies found in autoimmune disease—in other words, to the antibodies the normal immune system does not allow to be made," Haynes said.

The results provide a new goal for future HIV research, Haynes said. "We can focus on trying to redirect the response to HIV outer coat proteins from innate B cells to adaptive B cells. Alternatively, we can develop ways to induce that first line of polyspecific antibody defense during vaccination, if these antibodies are not harmful to those being vaccinated," Haynes said.

"We now have a window into how to study HIV vaccines from the host side of the problem," he said.

Collaborators on the study include Judith Fleming, William St. Clair, Richard Scearce, Kelly Plonk, Herman Staats, Thomas Ortel, Hua-Xin Liao and Munir Alam of Duke; Herman Katinger, Gabriela Stiegler and Renate Kunert of the Institute of Applied Microbiology, University of Agriculture, Vienna, Austria; and James Robinson of the Tulane University School of Medicine. The National Institute of Allergy and Infectious Diseases of the National Institutes of Health supported the work.

For more information, contact: Becky Oskin, Medical Center News Office (919–684–4148 dukemednews@contact.duke.edu

GLOBAL HEALTH RESEARCH BUILDING

Richard Frothingham, M.D.

Director, Global Health Research Building
Phone: (919) 684–5279
E-mail: richard.frothingham@duke.edu

Barton F. Haynes, M.D.

Director, Southeast Regional Center of Excellence for Emerging Infections and Biodefense
Director, Duke Human Vaccine Institute
Phone: (919) 684–5279 Larry Freeman

Larry Freeman

Operations Manager, Global Health Research Building and Southeast Regional Center of Excellence for Emerging Infections and Biodefense
Phone: (919) 681–1095
E-mail: larry.freeman@mc.duke.edu

Media Contact

For assistance in setting up interviews with Global Health Research Building researchers and administrators, please contact Becky Oskin in the Medical Center News Office at (919) 684–4148 or (919) 684–4966 or via e-mail at becky.oskin@duke.edu.

Overview

In 2003, the National Institutes of Health (NIH) approved funding for construction of a regional biocontainment laboratory at Duke University Medical Center. The new Global Health Research Building (GHRB), set to open its doors in May 2006, represents the beginning of a new era in research on emerging infections and biodefense.

The GHRB will serve as one of four regional laboratory facilities for a consortium of researchers from six universities in the Southeast, all charged with developing new vaccines, drugs and diagnostic tests designed to target infectious diseases.

Recent events, such as the intentional distribution of anthrax spores through the U.S. Postal System in 2001, the worldwide spread of the SARS virus in 2003 and even this year's deadly flu season, have signaled the need for further research targeting emerging infectious diseases and biodefense.

Duke University Medical Center will lead the consortium in its research and development efforts and will also provide a training center for investigators. Additionally, the GHRB will be ready to assist in response to any national or regional biodefense emergencies.

Program Highlights

The Southeast Regional Center of Excellence for Emerging Infections and Biodefense (SERCEB) is an NIH-funded consortium of six universities in the Southeast (Duke, the University of North Carolina at Chapel Hill, Vanderbilt, the University of Alabama at Birmingham, the University of Florida and Emory). Duke is the lead institution of the consortium. Additionally, 22 other southeastern institutions are affiliated with SERCEB and will be collaborating with the six primary universities to conduct valuable research. Local affiliate institutions include North Carolina Central University, North Carolina State University and East Carolina University. These institutions will have access to SERCEB resources.

The NIH has funded eight Regional Centers for Excellence nationwide. The GHRB will support the SERCEB as a regional laboratory dedicated to research, training and emergency response.

The GHRB will provide extensive benefits both to the field of research into infectious diseases, as well as to the community. Some of these benefits include:

• Additional biocontainment space that will be made available to the Durham County Public Health Department in times of need. For example, should SARS, influenza, or another public health emergency overwhelm the capacity of the Durham County Public Health Department, the GHRB laboratories will be available to director Brian LeTourneau and his staff for use.

• New state-of-the-art facilities for cutting-edge research to develop vaccines, drugs and diagnostics against emerging infections such as tuberculosis, SARS and influenza. The research teams at the GHRB will be available to rapidly develop diagnostics and vaccines for any new local and regional threats. These resources will be available to Duke, UNC-Chapel Hill, North Carolina Central University, North Carolina State University and East Carolina University researchers.

• Education programs in biosafety, infectious diseases, immunology and public health, targeted to investigators in the Triangle area who would like to enter the emerging infections and biodefense fields, and for investigators and their staff who need training in biosafety. SERCEB training programs will recruit women and minorities in particular into career development tracks.

Facilities

The GHRB will be housed in a 33,000-square-foot space on the medical center research campus. The cost of building the GHRB will be roughly $18 million, of which $6 million will be contributed by Duke with the additional $12 million coming from the NIH.

The GHRB will conduct only BSL2 and BSL3 research. Duke researchers have conducted research safely at these biosafety levels for over 35 years. BSL3 labs are currently in operation in multiple universities, institutions, and hospitals in the Triangle. Biosafety levels are described in detail in the Frequently-Asked-Questions (FAQs) below.

The GHRB will apply the most stringent interpretation of Federal guidelines for the design and operation of biosafety facilities. All steps have been taken to ensure that the GHRB meets or exceeds every current standard for BSL2 and BSL3 research safety. Some examples of the safety features include:

• Total direct exhaust from BSL3 laboratories (no recirculation).

• High-efficiency filtration of exhaust air.

• One-hundred percent redundancy for mechanical, electrical and plumbing systems.

• "Shower-out" facilities in the building.

• Twenty-four hour security presence in the building.

Frequently Asked Questions (FAQs)

Q: What type of research will be done in the GHRB, in a nutshell?

A: The GHRB will be used to develop new treatments, diagnostic tests, and vaccines for infectious diseases. All GHRB research will be related to human health. The results of GHRB research will be published in peer-reviewed scientific journals available to the public. Our mandate from the NIH focuses on emerging infections and biodefense.

Q: What are some examples of emerging infections?

A: The most important emerging infection in our lifetime was HIV/AIDS. Unrecognized before 1981, HIV has spread globally to become a top ten cause of death on every continent. Duke has been a leader in HIV research for over 20 years.

Recent emerging infectious diseases include SARS, West Nile Virus and avian influenza. Modern air travel has made our world more connected than ever before, so emerging infections like these have the potential to spread more rapidly. SARS was first recognized in Asia in March 2003, but spread within weeks to Europe and

North America. The first West Nile Virus cases in the western hemisphere were identified in New York City in 1999. Cases are now found from coast to coast. Avian influenza (bird flu) swept through poultry flocks in Southeast Asia in January 2004. A small number of humans have been infected, but a high proportion of the human cases have been fatal.

The examples of HIV, SARS, West Nile Virus and avian influenza demonstrate the need for a global response to protect American populations from emerging infections. The GHRB will contribute to this response.

Q: What is biodefense?

A: Biodefense is a broad program with the goal of protecting human populations against people who may want to hurt us using microbes. The need for biodefense became clear after 22 Americans were infected by anthrax spores delivered through the U.S. Mail. The GHRB will be used to develop new treatments, diagnostic tests, and vaccines to protect human populations from biological agents.

Q: What is a microbe?

A: Microbes include bacteria, viruses and fungi. The vast majority of microbes are harmless. In fact, life as we know it is dependent on the microbes that surround us. However, microbes also include the germs that cause human infectious diseases. Research in the GHRB will be limited to BSL2 and BSL3 microbes. These levels of research are currently being conducted safely at Duke and many other Triangle institutions.

Q: What do these Biosafety Levels mean?

A: BSL1 is the minimal level of laboratory safety used for microbes that don't cause disease in healthy adults. Laboratory strains of E. coli are handled at this level. BSL1 work can be safely conducted in a high school science laboratory with no equipment beyond a sink for hand-washing.

BSL2 is used for routine microbes that are present in our community and can cause human disease of varying severity. Examples of BSL2 microbes include hepatitis viruses and common causes of pneumonia such as the pneumococcus bacterium and the influenza virus. Human blood samples are processed at BSL2, so this safety level is used for routine tests in hospital and clinic laboratories.

BSL3 is used for microbes that can be transmitted by an aerosol, and that can cause serious or lethal infections in humans. The bacteria that cause human tuberculosis are handled at BSL3. This is the highest level that will be used in the GHRB. BSL3 laboratories maintain negative air pressure relative to the outside and to the rest of the building. Exhaust air from a BSL3 laboratory is not re-circulated to other parts of the building. Community hospitals typically have a single BSL3 room as part of their clinical laboratory suite.

BSL4 is used for dangerous and exotic microbes that pose a high risk of serous or fatal disease to researchers. Examples include smallpox and Ebola virus. Workers in BSL4 laboratories are protected by special suits ("space suits") with a dedicated supply of outside air. The GHRB will not contain BSL4 labs, and no BSL4 microbes will be handled at Duke.

Senator BURR. Mr. Wright.

Mr. WRIGHT. Mr. Chairman, thank you. First, I would like to commend this committee for its focus on the vital legislation which brings us here today.

PharmAthene was founded to develop countermeasures for bioterrorism. It has made significant progress in developing products which prevent and treat anthrax and agents of chemical warfare. In two short years, we have brought two products forward to a stage where they soon could be acquired by the Strategic National Stockpile. In bringing these two products forward, PharmAthene has had experience with BioShield I, the NIH, DARPA, and other DOD agencies.

There are many critical issues that need to be resolved for Project BioShield to be as effective as possible. Today, I am here to address the issue commonly referred to as the Valley of Death. This abrupt funding gap after proof of concept and before the procurement poses three serious problems. One, it prevents promising technologies from ever being developed. Two, it keeps large pharmaceutical companies and biotech companies from entering this

field. And three, it dramatically slows the development of products our Nation urgently needs.

Now, our firm has had experience with this issue, as I will illustrate with two products in PharmAthene's portfolio. The contrast between our experience with BioShield and the DOD process, I submit, could be helpful to this committee in drafting legislation for BioShield II.

PharmAthene's lead product, Valortim, has demonstrated significant efficacy in preventing and treating anthrax and will become an important part of the U.S. arsenal to combat this devastating terrorist threat. Some background here on Valortim™ should be helpful.

Valortim™ was originally discovered in Medarex's laboratories, and despite its promising potential, it languished unfunded in their labs due to the funding gap known as the Valley of Death. Despite BioShield, products such as this do not receive adequate funding because there are no clear-cut coordinated provisions for the funding gap between proof of concept and the stockpile. While PharmAthene in this instance was able to step in with necessary funding to pull Valortim™ out of the Valley of Death, there was invaluable time lost. This product could be in the National Stockpile today. However, even with all PharmAthene's best efforts, it will take us nearly 18 more months to deliver Valortim™ to the National Strategic Stockpile.

In contrast to our experience with Valortim™, we at PharmAthene have developed a product called Protexia™, an effective countermeasure to chemical and nerve gas threats which has gained critical support from the DOD. The DOD has been looking for a better way to protect its warfighters from chemical threats on the battlefield. They announced their interest through what is referred to as a Broad Area Announcement. The DOD process includes a step called Milestone A, whereby qualified companies are provided financing through proof of concept. This is very similar to the BioShield mechanism as provided by the NIH.

The critical difference that I am here to highlight is that the DOD has a Milestone B process that kicks in upon successful completion of Milestone A. The DOD through this Milestone B process provides funding to fill the gap. This facilitates the development of a company's product through manufacturing, human safety, and further animal efficacy studies. Therefore, it totally precludes the Valley of Death from entering into the process. As a consequence of Milestone B, Protexia™ will experience an uninterrupted flow in development and funding from proof of concept all the way to procurement.

I strongly recommend that as the committee considers legislation for BioShield II, that you support programs to provide funding for promising products from proof of concept through procurement, thereby eliminating the Valley of Death. I am confident that in your doing so, you will provide both incentives to companies to focus their resources on the critical needs spawned by bioterrorism as well as increase the likelihood that those who do will be successful in their endeavors. Thank you.

Senator BURR. Thank you, Mr. Wright.

[The prepared statement of Mr. Wright follows:]

PREPARED STATEMENT OF DAVID P. WRIGHT

Mr. Chairman, members of the committee: I commend this committee for its focus on the vital legislation which brings us together today.

I am David Wright, President and CEO of PharmAthene.

PharmAthene was founded to develop countermeasures for bioterrorism and has made significant progress in developing products which prevent and treat anthrax and agents of chemical warfare. In 2 short years, we have brought two products forward to a stage where they could soon be acquired for the Strategic National Stockpile.

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There are many critical issues that need to be resolved for Project BioShield to be as effective as possible.

Today, I am here to address the issue commonly referred to as the Valley of Death. This abrupt funding gap—after proof of concept and before procurement poses three serious problems:

1) It prevents promising technologies from being developed.

2) It keeps large pharmaceutical and biotech companies from entering this field; and

3) It slows the development of products our Nation urgently needs.

Our firm has had experience with this issue as I will illustrate from two products in PharmAthene's portfolio. The contrast between our experience with BioShield and the DOD process, I submit, could be helpful to this committee in drafting legislation for BioShield II.

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While PharmAthene, in this instance, was able to step in with the necessary funding to pull Valortim™ out of Valley of Death, there was invaluable time lost. This product could have been in the Stockpile TODAY. However, even with all of our best efforts it will take us nearly 18 more months to deliver Valortim™ to the Strategic National Stockpile.

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The critical difference, that I am here to highlight, is that the DOD has a Milestone B process that kicks in upon successful completion of Milestone A. The DOD through this Milestone B provides funding to fill the gap. This facilitates the development of a company's product through manufacturing, human safety and further animal efficacy studies. Therefore, it totally precludes the Valley of Death from entering into their process. As a consequence of Milestone B, Protexia™ will experience an uninterrupted flow in development and funding from proof of concept all the way to procurement.

I strongly recommend that as the committee considers legislation for BioShield II, that you support programs to provide funding for promising products from proof of concept through procurement—thereby eliminating the Valley of Death. I am confident that your doing so will both provide incentives to companies to focus their resources on the critical needs spawned by bioterrorism as well as increase the likelihood that those who do will be successful in serving our Nation's interest. Thank you.

Senator BURR. Dr. Russell.

Dr. RUSSELL. Thank you, Mr. Chairman. Good afternoon. I am Phillip Russell, a retired U.S. Army Major General. Up until recently, I served as a special advisor to the Department of Health and Human Services on the acquisition of medical countermeasures

for biodefense. I appreciate the opportunity to appear here this afternoon to provide my personal views on the challenges involved in the research, development, and acquisition of medical countermeasures.

Based on my many years' experience in the research, development, and acquisition of vaccines and drugs for the Army and for the Department of Defense and my more recent experience in HHS, including the procurement of smallpox vaccines and the initial BioShield contracts, I have done an analysis of the major factors that determine the success or failure of acquisition efforts.

Eight major factors that in the past have been critical to the success of the major acquisition of a medical product include, first, a credible threat determination and threat analysis. That is the primary basis for procurement of countermeasures, and as was said earlier, it is a DHS responsibility and it is yet incomplete for all of the threat agents except the initial big three, anthrax, smallpox, and botulism.

Second, a defined deployment and utilization for the product is needed. This is Health and Human Services responsibilities.

Both of these above factors provide the basis for the third factor that is essential for a BioShield acquisition, and that is governmentwide agreement on the requirement, including the amount of purchase. This consensus is needed under the current system for approval and release of BioShield funds by the White House. It will be increasingly difficult to achieve that in the future because of the differing views of the level of threat for agents past the big three.

A fourth requirement is a mature science base demonstrating proof of principle and evidence for the ability to manufacture the product. This is needed to provide assurance that the product can eventually be licensed, which is, of course, a BioShield requirement. The Regional Centers of Excellence are providing a superior opportunity to fulfill the needs for a science base and move products up through the early stages of development, up to the point where, as was said, there is a problem in transition.

The fifth factor are funds and a funding mechanism for early and mid-stage industrial development. This, I understand, is a focus of this hearing and has been proven to be absolutely essential.

Sixth, sufficient acquisition funds or obligation authority to provide the incentive for industry. The BioShield Special Reserve Fund, I believe, fulfills this requirement very well for the present, but may need additional funds in the future. I don't believe that there are sufficient funds in there to go for the full 10 years that it is expected to.

Seventh, we found that consultation and support for the manufacturer from the acquisition agency and from the FDA to assist in meeting regulatory requirements has proven to be essential in all major acquisitions. This support needed especially for the small and medium-size companies has a very high personnel cost for the FDA. It is a major burden on the acquisition agency.

Finally, indemnification of the manufacturer has been proven to be necessary for the purchase of vaccines for use by the government.

There is room for improvement in all of the above critical elements of the BioShield acquisition process, but two areas stand out

in my view as the most needing improvement. Bridging the gap from laboratory-based research to the initial stages of industrial development is a difficult process. It is an expensive process and entails a high degree of risk. For products needed for biodefense, the government usually has to subsidize the process and share the risk with industry. This is especially true for the small biotechnology companies that control many of the innovative new products. The present process does not fully meet the needs, as evidenced by slow development of several anthrax therapeutic products to the point where they would be eligible for BioShield procurement.

The government needs a well-funded, aggressive program based on a complete thorough threat analysis and well-defined priorities that conducts a thorough technology watch for needed countermeasures and uses a rapid contracting process to support early development. A mechanism to provide indemnification for manufacturers early in the contracting process would serve to remove a major disincentive for industry and would simplify the acquisition process for the contracting agency.

Thank you for the opportunity to be here today and I will be happy to answer any questions.

Senator BURR. Dr. Russell, thank you very much.

[The prepared statement of Dr. Russell follows:]

PREPARED STATEMENT OF PHILIP K. RUSSELL, M.D.

Mr. Chairman, members of the subcommittee, thank you for the opportunity to appear here today and provide my views on ways to improve the capability of the U.S. Government to develop and acquire medical countermeasures urgently needed to protect our citizens against the bioterrorism. I am Dr. Philip Russell, a retired Army Medical Corps Major General. From November 2001 until August 2004, I served as a senior advisor to the Department of Health and Human Services. In that capacity I was deeply involved in the acquisition of several medical countermeasures including the ACAM 2000 smallpox vaccine, Intravenous Vaccinia Immune Globulin, Equine antitoxin for Botulism, the rPA (recombinant protective antigen) anthrax vaccine, anthrax treatment products as well as the H5N1 influenza vaccine. As acting Director of the Office of Research and Development Coordination within the Office of the Assistant Secretary for Public Health Emergency Preparedness I was responsible for coordination of the initial purchases made under Project BioShield.

Drawing on my recent experience with some successful and some less-than-successful acquisitions under project BioShield and earlier HHS acquisitions, as well as my previous experience with research development and acquisition in the Department of Defense, I have done an analysis of critical factors that determine the outcome of major medical countermeasure acquisition programs. That analysis is the basis of my testimony today. I am providing this perspective with the intent to inform future legislative efforts intended to improve the capability of the government to obtain the medical countermeasures essential to national security.

I have identified eight critical elements that are major determinants of success or failure of a major acquisition under the current process and rules governing BioShield acquisitions.

- A credible threat determination and threat analysis.
- A defined deployment and utilization policy for the product.
- Governmentwide agreement on the requirement.
- A mature science base demonstrating proof of principal and ability to manufacture.
- Funds and funding mechanism for early and mid-stage industrial development.
- Sufficient acquisition funds (obligation authority) to provide the incentive for industry.
- Consultation and support for the manufacturer from the acquisition agency and the FDA to assist in meeting regulatory requirements.
- Ability to indemnify the manufacturer.

A generally accepted understanding of the threat and broad consensus on the policy for emergency use of the products was the basis for the successful acquisition of smallpox vaccine and enabled the botulism antitoxin and the rPA anthrax vaccine programs to proceed rapidly. Threat analyses and agreement on utilization policies are necessary to support and properly size product requirements and are lacking for the other agents on the CDC "A" list. Threat determination and threat analysis is the responsibility of the Department of Homeland Security. Utilization policy is the responsibility of HHS.

A consensus among the three major departments, HHS, DHS, DOD and White House offices on the proposed utilization policy and the size of the requirement is necessary to initiate a purchase under the BioShield program. This requires a process of interagency consultation which may go as high as the Deputies Committee. It was possible, albeit not easy, to obtain such a consensus for the botulism antitoxin and anthrax countermeasures where the threat was very clear. For future products against other threat agents, such as plague, tularemia and hemorrhagic fever vaccines, where both the threat analysis, and the size of the requirement and utilization policy will be much more challenging, this process may fail.

The existing NIAID program is creating solid scientific bases for future potential products. The investments in the Regional Centers of Excellence will provide the research basis for the potential development of a large number of new vaccines and therapeutics. Whether the potential products are eventually developed depends on whether funding is available for industrial product development to the point where they are considered viable candidates for a BioShield acquisition.

Most of the biologic products now in advanced development and under contract for purchase required major investments by the government during the early and mid stages of development prior to the purchase contract. This includes the ACAM2000 smallpox vaccine and botulism antitoxin developed under CDC contracts, and rPA anthrax vaccine and the next generation MVA smallpox vaccine developed under NIAID cost?reimbursement contracts. When adequate government support of early and mid level development is lacking, products will not progress to the point where they can be purchased under BioShield. The present process does not fully meet the needs of the government as evidenced by the slow development of anthrax treatment products to the point where they are eligible for BioShield procurement. Most small biotech companies with promising products need government support in the preclinical and early clinical phases of the R&D. Many large companies need government funding to share the risk of initial development for products where the government is the only market. This transition between laboratory research and early industrial development is one of the more serious and controversial problem areas in the current Federal program for developing and acquiring medical countermeasures.

The special reserve fund for purchases under BioShield is sufficient for the currently approved products but, looking to the future, it will certainly be insufficient for full 10 years. The high cost of bringing new products through the development and licensing process plus the cost of maintaining or renewing stockpiles and surge capacity will deplete the fund before the end of the decade. The permanent definite nature of the appropriation does provide confidence that the government acquisition agency will be able to honor the terms of contracts.

Differences in policy regarding buying products prior to FDA licensure, in addition to Economy Act requirements and issues of indemnification will make it difficult and may make it impossible to make joint HHS–DOD acquisitions of future important products such as botulism, plague and tularemia vaccines. The high cost of product development and economies of scale in production make joint acquisition highly desirable for certain products but experience indicates it probably cannot be done under existing policies for acquisition and indemnification.

Small and medium sized companies that are attempting to develop and license a new vaccine or therapeutic product need substantial consultation and support from the acquisition agency and from the FDA to succeed in meeting regulatory requirements. The requirements of the "Animal Rule" are a special challenge for small companies. Providing effective support and guidance requires a large commitment of qualified technical personnel especially from the FDA.

Indemnification of the manufacturer when products such as vaccines are used in a government program is essential. It is a major issue with every acquisition and manufacturers cannot be expected to deliver products to the stockpile without reasonable protection from liability. Inability of the acquisition agency to provide assurance of indemnification at the initiation of a contract is a very strong disincentive to large corporate manufacturers.

In summary, there are many improvements that should be made in the processes used to develop and stockpile medical countermeasures. Probably the most impor-

tant is the need to address the gap between laboratory-based research and advanced industrial development under BioShield. A program based on prioritized requirements that carries out a systematic technology watch and provides adequate funds for early and mid stage development of promising new products would greatly enhance the effectiveness of the BioShield program.

Perhaps equally important is a solution to the indemnification issue that would greatly simplify the contracting process for both the acquisition agency and the manufacturer. The current processes are cumbersome, expensive, and slow, a very strong disincentive to large corporations and a burden to the small companies.

A simplified process for determining requirements for products may be needed to address the very complex problem of obtaining the necessary government wide agreement on the need and utilization policy for such products as botulism, plague and viral hemorrhagic fever vaccines.

Thank you very much for the opportunity to provide this testimony. I will be happy to answer any questions.

SUMMARY

I am Dr. Philip Russell, a retired Army Medical Corps Major General. From November 2001 until August 2004, I served as a senior advisor to the Department of Health and Human Services. In that capacity I was involved in the acquisition of several medical countermeasures including the ACAM 2000 smallpox vaccine, Intravenous Vaccinia Immune Globulin, Equine antitoxin for Botulism, the rPA (recombinant protective antigen) anthrax vaccine, anthrax treatment products as well as the experimental H5N1 influenza vaccine. I was responsible for coordination of the initial purchases made under Project BioShield.

Drawing on my recent experience with some successful and some less-than-successful acquisitions under project BioShield and earlier HHS acquisitions, as well as my previous experience with research development and acquisition in the Department of Defense, I have analyzed the factors that determined the outcome of major medical countermeasure acquisition programs and have identified eight critical elements that are major determinants of success or failure of a major acquisition under the current processes and rules governing BioShield acquisitions.

- A credible threat determination and threat analysis.
- A defined deployment and utilization policy for the product.
- A mature science base demonstrating proof of principal and ability to manufacture.
- Governmentwide agreement on the requirement.
- Funds and funding mechanism for early and mid-stage industrial development.
- Sufficient acquisition funds (obligation authority) to provide the incentive for industry.
- Consultation and support for the manufacturer from the acquisition agency and the FDA to assist in meeting regulatory requirements.
- Ability to indemnify the manufacturer.

There is room for improvement in all of the above elements of the acquisition process but two elements stand out as needing legislative action. A critical deficiency has become apparent in the funds and mechanism to support early and mid stage development of products to the point where they are considered eligible for a BioShield procurement. The current process for indemnifying manufacturers of vaccines for government use in biodefense is a disincentive to both large and small companies and should be changed.

Senator BURR. Mr. Scott, is it Magids?

Mr. MAGIDS. Magids, hard "G".

Senator BURR. Mr. Magids.

Mr. MAGIDS. Mr. Chairman, my name is Scott Magids. Thank you for the opportunity to appear here today to provide my views on ways to enhance the development and commercialization of countermeasure technologies needed to protect our country.

I direct the University of Maryland's Technology Advancement Programs, referred to as TAP. By way of background, I have been an entrepreneur and venture capital investor in various technical markets. At the University of Maryland, I have served as an architect of a plan to increase technology commercialization at our institution and throughout the Washington region, including in the area

of biodefense. Technology entrepreneurship activities at our university, including TAP, are centralized within the Maryland Technology Enterprise Institute, referred to as MTECH, a unit of the Clark School of Engineering.

We recognize that the commercialization of innovations is a catalyst for economic growth and advancements in areas like health care and national security. A significant gap exists between technology creators and viable commercial enterprises. Three principal factors cause this gap.

Professional management talent is not readily available to most technology creators, and an adequate amount of C-stage funding currently exists and many technology creators are not sufficiently motivated or educated in business-related topics to commercialize their inventions. The Clark School has developed and implemented a plan to increase technology commercialization. This plan encompasses education, hands-on support and access to funding, communications initiatives, operating initiatives, and entrepreneurial culture building. I will briefly describe each of these elements and share some of our results.

We educate technology creators at our institution and throughout our region about the commercialization process, marketability of research, and benefits of bringing innovations to customer markets. We selectively admit two to four new high-potential technology start-ups into our TAP program each year. We regularly work with innovators in the homeland security, medical device, pharmaceutical, and biosensor markets. We apply a rigorous company-building process to these ventures encompassing planning, team building, product road maps, and IP protection.

In addition, we help bridge the seed funding gap by building a thorough investment process and relationships with angel and venture capital investors, assisting our companies in preparing for, negotiating, and closing funding transactions, coaching our companies in applying for Federal grants, and acting as a liaison to our State's venture fund and the Clark School's MIPS program, which provides value-add R&D funding to start-ups, particularly in the biodefense area.

Communications play an important role in our commercialization plan. Communications energize our local business community to support commercialization, and communications depicting success stories motivate other innovators to follow suit, as success breeds success. These communications initiatives spread the message within our institution and throughout our region that commercialization is beneficial and feasible.

As an example, several of our TAP companies have been started by NIH scientists. We have also taken steps internally to support commercialization. We have recruited individuals with deep entrepreneurial and venturing experience. We have developed a compensation policy for TAP, which includes current revenue, deferred revenue, and equity interest, and we have become sensitive to the often competing goals of technology creators—continue to advance in their fields of research or pursue commercialization. And we have created unique approaches to navigate these issues.

The final element of our plan is an entrepreneurial culture. Senior leadership within our institution encourage entrepreneurial ac-

tivity among technology creators and provide positive recognition for such efforts.

I will conclude by highlighting some of our results. TAP companies have created over 1,700 jobs and raised $260 million in private funding. Two of our biotechnology firms have gone public and have generated meaningful revenues, and these firms currently have a combined market value of over $1.6 billion. Roughly 70 percent of companies graduating our program continue material operations after 5 years. Approximately one new faculty company is being started each quarter at our institution, and our programs have received regional and national recognition as we regularly advise other institutions regarding innovative technology commercialization approaches.

I will look forward to your questions.

[The prepared statement of Mr. Magids follows:]

PREPARED STATEMENT OF SCOTT MAGIDS

Introduction

My name is Scott Magids. I am the director of the University of Maryland's Technology Advancement Program ("TAP"), a unique program designed to stimulate the commercialization of innovations through new venture creation. I am honored to submit written and verbal testimony to this esteemed subcommittee. By way of background, I have worked as an entrepreneur in the technology and market research industries, and as a venture capital investor and management consultant in various high-technology markets. I also teach college courses in technology entrepreneurship. I have served as a principal architect and executor of a strategic plan to increase technology commercialization at the University of Maryland as well as in the surrounding region.

The TAP Program resides within the Maryland Technology Enterprise Institute ("MTECH"). MTECH is the vehicle for entrepreneurship and outreach for the University of Maryland's Clark School of Engineering ("Clark School"), a nationally-recognized engineering college.

TAP helps bridge the gap between technical inventor and viable early-stage company by providing extensive hands-on business support; access to seed and early-stage funding; technical expertise, namely to support product development; and low-cost infrastructure. TAP supports firms in a range of markets, including biosensors, software, homeland security, pharmaceuticals, medical devices, and information technology. TAP is a key part of a comprehensive effort within the Clark School to increase technology commercialization at the University of Maryland and in the surrounding region, and this effort also includes other initiatives described below.

TAP has enjoyed significant success since its creation in 1985. As examples of our success, TAP-supported companies have created 1,790 jobs and raised $260 million in angel and venture capital funding, including $15 million between 2004–present.

Rationale for the University of Maryland's Technology Entrepreneurship Programs

Effectively commercialized technical innovations are a key catalyst for economic growth, productivity enhancements, and advancements in healthcare, public safety, and national security. In most parts of the country, including the Washington, DC region, **a significant gap exists between an individual technology creator and a viable early-stage company capable of bringing technology-based products to the marketplace. This gap exists for three principal reasons:**

- **Professional management talent, with expertise in fundraising, business planning, and team-building, is not readily available to most technology creators;**
- **An inadequate amount of seed-stage (pre-prototype) funding exists for product development and startup working capital; and**
- **Many technology creators are not sufficiently motivated or educated in business-related topics to comfortably commercialize their inventions.**

Unfortunately, this gap stymies the advancement of potentially high-impact technologies from the laboratory to the customer marketplace.

The University of Maryland's Clark School of Engineering has closely examined these obstacles, and has attempted to develop a comprehensive plan to accelerate technology commercialization, through venture creation, at the university and in the surrounding region. This plan encompasses five components: (1) education; (2) hands-on support and funding access; (3) internal and external communications; (4) operating initiatives; and (5) entrepreneurship culture-building.

University of Maryland's Technology Entrepreneurship Initiatives

EDUCATION

Technology commercialization begins with education. The goals of education include helping technology creators understand the commercialization process; allaying fears regarding commercial endeavors; and encouraging technologists to pursue commercialization. MTECH, the Clark School's entrepreneurship unit, offers four types of education: (1) Seminars and symposiums for faculty and students, with topics including IP protection and marketability of research; (2) Entrepreneurship courses for technical students; (3) An annual Technology Startup Boot Camp, open to technology creators throughout the region; and (4) An annual Business Plan Competition in which technical teams, from the University of Maryland, compete for cash prizes and receive intense mentoring from successful entrepreneurs.

HANDS-ON SUPPORT AND ACCESS TO FUNDING

Hands-on support and access to seed-stage funding are critical to crossing the bridge between innovator and viable enterprise. **The TAP Program selectively admits two-to-four new startups each year pursuant to a thorough analytical process similar to professional investors' due diligence. During a typical 4-year incubation period, TAP applies a rigorous company-building process to help create well-managed, well-planned, properly-funded commercial ventures.** Acting as a coach, mentor, and marshal of resources, **TAP assists its companies with (1) business planning and market analyses; (2) product development support; (3) corporate structure and IP protection; (4) team-building, namely executive recruiting; (5) and capital formation.** TAP helps keep its portfolio companies on track to commercialization through weekly status meetings and consistent, hands-on participation.

TAP has developed a number of initiatives to overcome the funding gap its seed-stage companies encounter: (1) TAP has designed an investment process and built close relationships with angel investors and venture capital investors; (2) TAP closely supports the angel and venture fundraising process for its companies, including preparation, structure development, and terms negotiation; (3) TAP closely coaches its companies in applying for Federal and regional grants, namely for technology development; and (4) TAP acts as a liaison to other State of Maryland and MTECH funding programs, including the State of Maryland Venture Fund and the highly successful Maryland Industrial Partnerships (MIPS) Program, an R&D funding program also run by MTECH. The MIPS Program provides grants to Maryland startups, up to $150,000, to support technology and product development at a University of Maryland campus.

In addition to helping its companies aggregate capital, TAP also provides its firms valuable money-saving resources, including low-cost physical infrastructure; special lab facilities; access to bio equipment; and access to technical expertise through the university.

COMMUNICATIONS

Communications play two important roles in increasing the level of technology commercialization: (1) Communications encourage the business community and other technical institutions to support technology commercialization; and (2) Communications, depicting the success of inventors who commercialize their technologies, motivate other technology creators to consider commercial endeavors. MTECH and TAP proactively build relationships with service providers, senior personnel at other technical institutions, and investors. These persons play valuable roles as mentors, guest educators, sponsors, seed-stage capital providers, and/or referrals of technology creators seeking commercialization help. Furthermore, these persons help disseminate a key message in the regional technology and business communities: *Technology commercialization is ex-*

tremely important, beneficial, and feasible. As an example of the benefit of communications, several TAP companies have been started by NIH scientists.

OPERATING INITIATIVES

MTECH and TAP have implemented operating initiatives designed to support technology commercialization. First, MTECH has recruited persons with significant venture capital and company operating experience to manage TAP and other MTECH programs. Likewise, TAP receives equity interests, deferred revenues, and current revenues from its portfolio companies, and this compensation approach helps to align the interests of all parties involved in technology commercialization. Generally, TAP receives 1–4 percent of the fully-diluted equity interests of its firms per year of participation in TAP, and most startups remain in TAP an average of three years. Likewise, deferred revenues generally accrue at a rate of $1,000–$3,000 per month and are payable at the earlier of (1) a qualifying event such as material revenues, a significant equity financing, or a sale of the company; or (2) two years following completion of the TAP Program. MTECH reinvests these proceeds into TAP and its other entrepreneurship initiatives. Finally, MTECH and TAP have become sensitive to the competing goals of many technology creators seeking commercialization—continue to advance within their technical fields and pursue commercial ventures. Approaches have been designed to help navigate these issues.

ENTREPRENEURSHIP CULTURE

The final component requisite for technology commercialization is an entrepreneurial culture. At the Clark School, several factors have contributed to the development of an entrepreneurial culture in which technologists are motivated to pursue commercialization: (1) Senior leadership within the Clark School encourage entrepreneurial activity and positively recognize such effort; (2) Communications efforts led by MTECH widely promote success stories (e.g. of TAP companies) internally and to other members of the technology community, as "success breeds success;" and (3) Most importantly, consistently exposing technologists to experienced businesspersons; commercialization education; and company-building processes inspires inventors to pursue commercialization.

Results

The TAP Program has enjoyed significant success during the past 20 years: (1) 1,790 jobs have been created; (2) $260 million in angel and venture funding has flowed into TAP firms; (3) Approximately 70 percent of TAP firms "graduating" from the program continue material operations 5 years post-graduation; (4) TAP firms have received over $70 million in Federal grants; and (5) Two TAP biotech firms have gone public on the NASDAQ, and these firms have a combined current market capitalization of $1.6 billion. TAP has been well received at the University of Maryland and in the regional marketplace, as 396 firms have sought admission into TAP, and 68 firms have been accepted into the program. In addition, the level of entrepreneurship activity within the Clark School has increased significantly, as approximately one new faculty or student firm is formed each quarter, and a number of successful technology firms have been formed by faculty in recent years. TAP and other MTECH entrepreneurship initiatives have received local and national recognition, and numerous universities and research institutions have solicited MTECH's assistance in creating similar programs.

Senator BURR. Dr. Frothingham, I truly am thankful that you would come up, impressed with the work that is done by you and specifically Duke University and, quite honestly, all of the academic points in North Carolina that are on the front line of a lot of the research. I am encouraged at the approach that you outlined in your testimony.

Beyond the moneys that NIH specifically provides, what are the other sources of money to support the ongoing and proposed work within this regional effort?

Dr. FROTHINGHAM. I think you put your finger on the problem right there. We are most familiar, as academic researchers, with the NIH and that is where we get most of our funding. We have some ideas about funding mechanisms that NIH might employ.

We certainly do attempt to work with companies, and there is an Office of Science and Technology at Duke that has been quite successful. We do spawn off biotech companies all over the Triangle, so those things do occur. Venture capital enters into these things.

But I think the current system under which I function as an academic researcher, I guess you could call it the traditional NIH grant structure, the RO1 format, the grants are reviewed based on their scientific merit and productivity is measured by publications in journals. So as an academic researcher, if I publish—if I discover, generate an important proof of principle and I get it published in a prestigious journal, then I have succeeded. That is my definition of success in my system. And this system has produced a lot of scientific knowledge. But we do need a different system, I think, an additional maybe supplementary system that is based more on milestones and deliverables.

Senator BURR. Currently, are there companies that have invested in your effort?

Dr. FROTHINGHAM. Yes, there certainly are. I don't have the names in front of me. In fact, some of these investments are not yet relationships that I am able to talk about. But certainly there has been success in that area. I alluded to some of the products without giving names or details in my testimony.

Senator BURR. Dr. Russell, again, we are appreciative that you would come. We are thankful of the many years of dedicated service that you have provided to the Nation in both uniform and out of uniform.

You gave us a powerful testimony to the specific things that are necessary to bring countermeasures to BioShield. You argued convincingly, I think, on the need to focus on the mid to latter stages of medical countermeasure development. In your opinion, who should be in charge of that?

Dr. RUSSELL. The National Institutes of Health have the greatest concentration of managerial and scientific talent and probably that organization is best suited to carrying out the mid and later stage medical countermeasure development. They did a very good job, for example, with the recombinant protective antigen and the MVA vaccine.

However, I would argue that we should look at the DOD model that separates the funding stream for early and mid-stage development from the funding stream that goes into the RO1 program and the Centers for Excellence and probably separate the management in a clear manner. The latter stages have to be very carefully coordinated with the HHS BioShield effort.

Senator BURR. You also mentioned indemnification. I guess I would ask you, what type of liability provisions do you believe we should have?

Dr. RUSSELL. I believe that is a legal question that I have no confidence in answering. But I would——

Senator BURR. No, but it is my job to goad everybody to try to answer it that I can. [Laughter.]

Dr. RUSSELL. I would mention that the Children's Vaccine Fund, the process that indemnifies companies for children's vaccines, I think is a model that should be looked at seriously in this regard.

Senator BURR. Thank you. Thank you.

Mr. Wright, I note from your background that you have held several positions in large pharma companies. Given that you have been on both sides of the fence, what, in your opinion, is keeping big companies out of biodefense?

Mr. WRIGHT. I don't think there is any one thing. I think it is a combination of some of the factors we have described this morning. Liability is certainly an issue. Incentives are a huge issue. Large pharmaceutical companies have shareholders and they have to make profits.

Senator BURR. In your opinion, can a company who participates in the research of biodefense products turn around and explain to a board and shareholders of a publicly-traded company successfully why they want to make an investment, why they want to research in that and put in that link that says, and here is what is on the back end? Is the system that predictable?

Mr. WRIGHT. I believe it is, especially if the back end is there, because——

Senator BURR. And I guess my question is, is it there now?

Mr. WRIGHT. No. It does not exist now. I mean, they cannot make the type of profits—it is not only profits, it is opportunity loss, because they are going to have to take resources from developing the products which provide their profits in order to do this. So there is an opportunity cost loss as well as a liability issue and there is really nothing in it for them.

Senator BURR. I don't want to downplay the potential out of academia or from the smaller biotech companies or anybody, but what do we lose, if anything, but not having big pharma engaged in this battle?

Mr. WRIGHT. One of the other key issues that small companies have in developing these products is manufacturing. They don't have—small companies like myself, we have no manufacturing facilities. We have to go look for contract manufacturers. The desire of the government is to have these products made in the United States. There is simply not available facilities to make these products in the quantities and in the time frames in the United States. Large manufacturers, large pharma has manufacturing. They have capabilities. They can make this stuff. They have got plants they can put online and many of them have capacity, but that capacity is not for sale.

Senator BURR. If you were forced to prioritize tax incentives, patent incentives, liability, intellectual property protection, how would you prioritize those in importance of us addressing to begin to pull more people in?

Mr. WRIGHT. I think if you want to pull the large pharma company in, that patent wildcard is critical. That is one thing that would do it. Now, Dr. Russell and I would probably disagree on the way to do this. In fact, I know we will because we have talked about it because there is a feeling that that is robbing from Peter to pay Paul, that the government should just up front pay people to do this.

But if we are looking for a way to interest a lot of people in coming into this area, patent wildcard will do it—critical. It is a way that these people can show their shareholders and their boards that there is a reason for doing this and there is a reason for taking the resources and the risk, because the risk, as you heard, is huge to go down this line.

The other thing that really would help would be a little bit more transparency, and while I totally agree that the RFP process is specific, the RFP process comes way too late, all right. By the time an RFP is issued, there may be one company that could qualify for it, whereas if companies today knew that in 5 years, the government would buy 500 doses of this, 3,000 doses of this, and 4,000 doses of this, or that they want this product to be a therapy, a vaccine, or whatever, then companies can say, can we get there? Can we put the resources? There is a market. There is a reason to do this.

Senator BURR. When the RFP is issued, is that the first point that a manufacturer knows what the potential volume is?

Mr. WRIGHT. There may be a hint in the RFI, which comes out traditionally 3 to 6 months before an RFP, but the first specific information is the RFP, yes, sir.

Senator BURR. Is a hint sufficient for venture capital to come?

Mr. WRIGHT. No, sir.

Senator BURR. Dr. Russell, am I wrong in believing—and I said in a speech this morning that our progress has to send us to a point where these countermeasures are developed in days, weeks, and months versus years based upon how the threat might evolve in the future. Am I off base on that?

Dr. RUSSELL. The development process for biologics and for drugs is a process that is very, very difficult to compress. The recent experience in trying to accelerate the development has managed to compress it from an average of 10 years down to a few years. But compressing it much shorter time than that is going to be very difficult, if not impossible, because of the time it takes to do the toxicology, all of the safety issues, the proof. It is a real time problem and it can't be compressed much more than it already is.

Senator BURR. But in your estimation, the future threats may challenge us to try to do that.

Dr. RUSSELL. It certainly will, sir.

Senator BURR. OK. Mr. Timmins, from your testimony, you described a fair bit of support from DOD in the development of your approach and specific countermeasures. What has been the interest from NIH in your products?

Mr. TIMMINS. We, like many small companies, go through the NIH granting process. We began doing that in earnest approximately 2 years ago. The NIH process is one where it is a little bit of a relationship-oriented process, so in our first attempts at grants there, we didn't have a high level of success, mainly because we were told we weren't a known entity within the granting process. Since that time, we have done a little better. We have hopes to do better going forward.

Certainly, though, in comparison, DOD has been quite proactive in expressing their wants, needs, and desires and support for what we are doing. So it is a little bit of a contrasting process.

Senator BURR. Given that list of potential incentives that I talked to Mr. Wright about, would you have picked a different incentive to be number one, other than patent?

Mr. TIMMINS. Sure.

Senator BURR. What would it be?

Mr. TIMMINS. Absolutely. I would have picked intellectual property protection, because the only assets that our company has are the people that walk up and down the stairs every day and our intellectual property. I am not worried about the people going away as much as I am worried about the intellectual property going away. So protection there for me is critical.

Second to that, but it is a far drop second, is liability protection. I talked a little bit about our clinical trial attributes, so I am not as worried about a safety issue as maybe a company dealing with more toxic technologies might be.

Third for me would be the patent incentives. Again, we have a platform technology, so nobody can do the same things we do using our patents. We have a pretty specific and narrowly-defined technology that we have carved out for ourselves.

And then fourth would be the tax incentives, simply because we don't pay any taxes yet, but we want to in the future—a lot. [Laughter.]

Senator BURR. I can't wait for the next opportunity that you are up sharing with me that you made a mistake on that. [Laughter.]

Scott, let me just ask you, what participation, if any, do large pharma companies have in the TAP program?

Mr. MAGIDS. They act as corporate investors in our companies and they are increasingly acting as seed investors in our companies and we initiate those relationships and structure those relationships on behalf of inventors, so we more or less end up acting as an intermediary, in one example, between an NIH scientist pursuing a new pharmaceutical business and a source of funding.

Senator BURR. Good. I want to thank this opportunity to thank all of our witnesses today, not just panel two but panel one again, too.

We started with a very interesting morning with a fire in the Rayburn House Office Building, as they shut down Independence Avenue and we stymied all the rush hour traffic to all be converted to the front of the Senate side. I should have known this was going to be a difficult day for us to maneuver through and I think that is indicative of the fact that we have got people who have not made it here who have been sending messages that they were coming, they were coming, they were coming—Chairman Enzi, Senator Kennedy, Senator Mikulski—and they haven't made it. That is indicative of how the day changes, and I know that we have got a vote that is coming up in the Senate in the next 20 minutes.

I want to thank you for the valuable information that you have been able to share with us. My hope was that at one time, midsummer, we would be in a position where we could actually take all the stakeholders, members, companies, agencies of the Federal Government, begin to look at language. I am not convinced that we are there yet and I believe that this process deserves us to be as thorough and as comprehensive as we feel we need to be.

So I think it begs that we will run into the month of July with additional hearings as we begin to try to refine some of the answers that we have gotten where maybe it hadn't completely sunk in for those of us that are asked to make the decisions.

It is also challenging to try to establish that this is a process that does not create winners and losers. Everybody has to be a winner, and most importantly, it is the public that has to win from this. Through what you have been able to share with us and what we can put in the form of legislation, we, in fact meet the challenge of having an effective biodefense program in this country. And I am confident that we have made tremendous progress in the first 5 months, but it will take several more months for us to get to a point that we can refine that into legislative language.

Again, I thank you for your willingness. I thank my colleagues for their interest, and this hearing is now adjourned.

[Whereupon, at 3:43 p.m., the subcommittee was adjourned.]

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